HEALTH SERVICES RESEARCH ON ENDOSCOPIC SURVEILLANCE FOR GASTRIC CANCER IN THE SINGAPORE CHINESE POPULATION

– Experiences of the Gastric Cancer Epidemiology Clinical & Genetic Programme

By

ZHOU HUIJUN

(M.B.B.S., MSc in Clinical Science)

A THESIS SUBMITTED FOR

THE DEGREE OF DOCTOR OF PHILOSOPHY

SAW SWEE HOCK SCHOOL OF PUBLIC HEALTH

NATIONAL UNIVERSITY OF SINGAPORE

2013

DECLARATION

I hereby declare that this thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.

ZHOU HUIJUN

Tuesday, April 15, 2014

ACKNOWLEDGEMENTS

I would like to express my sincere thanks and gratitude to the following people without whom my PhD and this thesis would not have been possible.

First and foremost, I would like to express my heart-felt appreciation to Prof. Lee Hin Peng for his inspiring guidance and insightful advice throughout my PhD study.

I am greatly indebted to Prof. Yeoh Khay Guan for his expert guidance in gastric cancer surveillance and his generosity for financial support.

I owe a great deal to Prof. Li Shu Chuen for his expert guidance in health services research and career development.

I am deeply grateful to my best friend Dr. Nasheen Naidoo for refining my manuscripts with his excellent academic writing skills and his unfailing encouragements.

I am deeply grateful to Prof. Dan Yock Young for his valuable instructions in Markov model construction and sincere support in my PhD pursuit.

Special thanks go to Prof. Jimmy So Bok Yan and Prof. Yong Wei Peng for referring their patients to my study

Thankful to team members of the Gastric Cancer Epidemiology Clinical & Genetic Program for their coordination and assistance in data collection

Last but not least, to School of Public Health for providing me with this opportunity to further my academic pursuit in the field of health services research.

TABLE OF CONTENTS

SUMMARY

Gastric cancer is largely a fatal disease associated with high incidence and mortality in most Asian populations where it imposes a huge disease and economic burden on the society. Given that the efficacy of gastric cancer treatment is still unsatisfactory, efforts have been directed at its prevention. Presently secondary prevention measures aiming for early detection, namely screening and surveillance, have assumed an increasingly important role for gastric cancer control.

Mass screening targets the asymptomatic subjects in the general population at high risk of gastric cancer. Surveillance focuses on the people with precancerous lesions who are therefore already in the process of gastric cancer development. Studies have demonstrated that both screening and surveillance are effective in detecting the malignancy at an earlier stage and consequently achieving longer patient survival. However, for public health practice to translate these research findings into health benefits, more information is needed to investigate the cost of illness, clinical outcome and ultimately cost-effectiveness ratio. These studies belong to health services research (HSR).

This PhD project was undertaken to conduct HSR studies on the secondary prevention of gastric cancer, particularly endoscopic surveillance. Besides its value as an academic pursuit, this PhD project aims to provide scientific evidence to address the issues regarding implementing an endoscopic surveillance program for gastric cancer in the Singapore Chinese population. The cost-effectiveness data may also help health authorities to make an informed decision on the worth of investing in such a public health program for Singapore.

Nested within the Gastric Cancer Epidemiology, Clinical and Genetics Program (GCEP), three studies were designed for this project. Each study has value in its own right and at the same time, they together form a coherent series to answer the overriding question of this project: Is endoscopic surveillance for gastric cancer cost-effective in the Singapore healthcare system? For the benefit of readers and reviewers, the thesis is organized into seven chapters as follows.

Chapter I introduces basic clinical and epidemiological knowledge about gastric cancer, and two commonly used clinical outcomes in cancer research, namely, survival rate and quality of life. Readers can catch an overview of gastric cancer. This chapter aims to convey the message that gastric cancer is of major public health significance in Singapore and worldwide.

Chapter II introduces the key definitions and concepts regarding gastric cancer prevention. The natural history of gastric cancer and the theory of secondary prevention are explained. I also summarize the current state of gastric cancer prevention highlighted by different studies.

Chapter III presents the first study of this project which is a cost of illness study based on empirical data from the GCEP in delivering endoscopic surveillance. Unlike a conventional cost of illness study which covers the clinical phase starting from diagnosis to post-diagnosis treatment until the patient's death, our study sheds light on the cost increment before the diagnosis, an area rarely touched to date. As a stand-alone cost analysis, we elucidated the mechanisms underlying the temporal trend of cost generation. Health policy makers can use this information in the planning of a long-term program. To enhance the coherence of this project, results have been directly used in the final model of the cost-effectiveness analysis.

Chapter IV presents the second study which is a quality of life study in Chinese patients with gastric cancer. We validated a gastric cancer specific quality of life instrument called Functional Assessment of Cancer Therapy-Gastric module (FACT-Ga). This validation study paves the way for future quality of life research for gastric cancer in Chinese populations. At the same time, the scores of the European Quality of Life Five Dimensions (EQ-5D) instrument derived by this study have been inputted to reflect the utilities of gastric cancer patients in the final cost effectiveness analysis.

The third study, a cost-effectiveness analysis using the Markov model, is presented in the subsequent three chapters.

Chapter V gives a detailed description about how the Markov model was built using TreeAge software. To highlight transparency as one of the key criteria for model validity, I have explained step by step the clinical assumptions and pros and cons of the data selected. Readers are able to have a clear picture about the model construction process from a simple diagram to a complicated Markov model.

Chapter VI presents the cost-effectiveness ratio and its heterogeneity at base case analysis. The input parameters are examined extensively by deterministic and probabilistic sensitivity analysis. Results are presented for the parameters with significant impact on net health benefit or probability of being cost-effective.

Chapter VII discusses the findings of the Markov model from the perspective of the healthcare system. The cost-effectiveness of 2-yearly endoscopic screening, annual endoscopic surveillance

and no endoscopic intervention were compared. The model recommended surveillance to be the cost-effective strategy in prevention of gastric cancer in Singapore Chinese. Several parameters are identified as influential factors for establishing a successful endoscopic surveillance program. Future research to improve predictability and precision of the current model is suggested.

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ASIR: Age Standardized Incidence Rate

ASMR: Age Standardized Mortality Rate

ASRS: Age Standardized Relative Survival

CI: Confidence Interval

EGC: Early Gastric Cancer

EQ-5D: European Quality of Life Questionnaire- 5 Dimensions

FACT: Functional Assessment of Cancer Treatment

FACT-Ga: Functional Assessment of Cancer Treatment – Gastric

- PWB: Physical Well-Being
- EWB: Emotional Well-Being
- SWB: Social Well-Being
- FWB: Functional Well-Being
- GCS: gastric cancer subscale

GC: Gastric Cancer

GCEP: Gastric Cancer Epidemiology Clinical & Genetic Program

GEE: Generalized Estimation Equation

H. pylori: Helicobacter Pylori

ICER: Incremental Cost-Effectiveness Ratio

NHB: Net Health Benefit

NUH: National University Hospital

OGD: Oesophago-Gastro-Deuodenoscopy

OR: Odds Ratio

PSA: Probabilistic Sensitivity Analysis

QALY: Quality Adjusted Life Year

QoL: Quality of Life

TNM System: Tumor Node Metastasis System

WTP: Willingness-To-Pay

CHAPTER I: GASTRIC CANCER BURDEN

1.1 Gastric Cancer - Definition and Classification

1.1.1 Gastric cancer definition

Gastric cancer (GC) refers to cancerous malignancy arising from any part of the stomach. In the literature and clinical practice, the term GC does not refer to a single disease, but rather different cancerous diseases affecting a single organ. Although GC is a heterogeneous disease covering lymphoma, leiomyosarcoma, carcinoid, adenocarcinoma and squamous cell carcinoma, the most frequently encountered histological type is mucosal adenocarcinoma which comprises more than 90% of all GC cases worldwide (Forman and Burley 2006) and locally in Singapore (Singapore Cancer Registry Committee 2010). Therefore, GC refers to the adenocarcinoma most of time in this thesis.

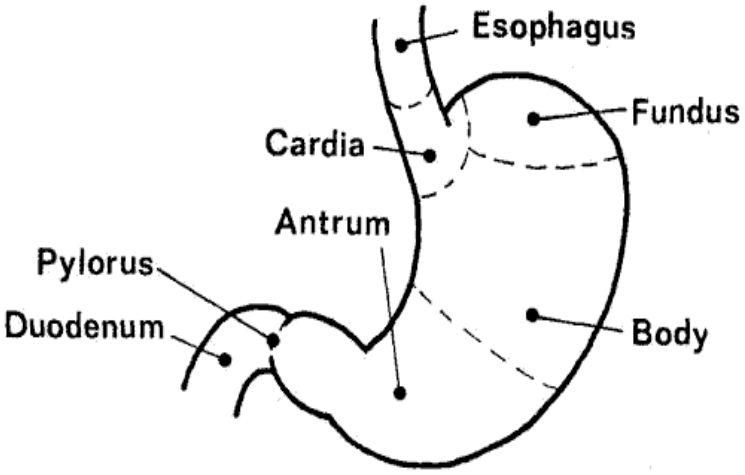


Figure 1-1. Anatomy of the stomach

The stomach is arbitrarily divided into five anatomical parts (Figure 1-1) labeled from proximal to distal ends as cardia, fundus, body, pylorus and antrum. These labels help us locate and describe GC lesions. The sites where GC occurs are also relevant to histological type and thus prognosis of patients. Table 1-1 summarizes the subsite distribution of GC in Singapore.

Table 1-1. Subsite distribution of gastric cancer in the stomach (2003-2007)

Subsite	Male	Female
Cardia	249	116
Pylorus	72	35
Antrum	268	187
Fundus	19	13
Body	77	61
Body (less curvature)	124	80
Body (greater curvature)	42	34
Other	68	29
Not otherwise specified	456	330

(Singapore Cancer Registry 2011)

1.1.2 Gastric cancer staging and histological classification

Cancer staging is a critical step in clinical management and cancer-based public health programs. The stage of a cancer patient measures the extent of disease spread and is related to treatment protocol, cancer progression and future prognosis.

1.1.2.1 TNM staging system for gastric cancer

Like most solid tumors, GC Stage is rated according to TNM system. TNM staging system was developed in 1940's and has been globally recognized as the international standard for cancer classification. Currently it is maintained by American Joint Committee on Cancer (AJCC). TNM staging system defines criteria to measure the severity of a tumor disease as follows.

1. T (tumor) refers to the size of the primary tumor mass, which could be the original tumor and/or nearby tissues when involved.
2. N (node) refers to lymph nodes close to the original organ or tissue. The cancer is called regional if nearby nodes are invaded.

3. M (metastasis) refers to tumor's spread to a distant organ or system

To facilitate the understanding how TNM system works with GC disease, the histology of stomach wall is presented in Figure 1-2. The detailed explanation of TNM system for GC is presented in Table 1-2.

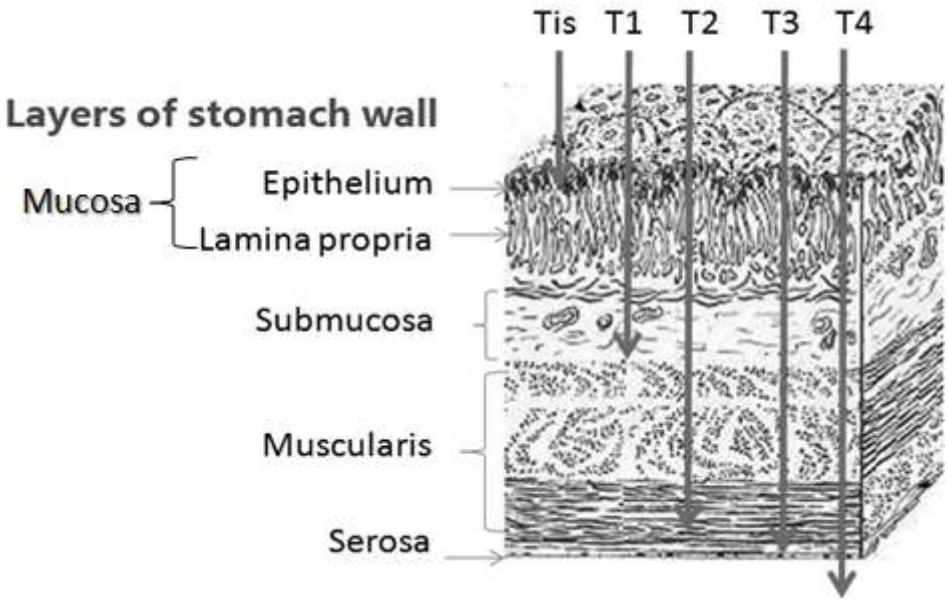


Figure 1-2. Histological layers of stomach wall

Table 1-2. TNM staging system for gastric cancer

Parameters	Description
Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria
T1	Tumour invades lamina propria, muscularis mucosa, or submucosa
T1a	Tumour invades lamina propria or muscularis mucosa
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	Tumour invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumour invades serosa (visceral peritoneum)
T4b	Tumour invades adjacent structures
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in 7-15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

(Washington 2010)

1.1.2.2 Clinical staging system for gastric cancer

Based on the TNM system, a clinical staging system was developed and adopted by clinicians. The two systems are used in parallel in clinical practice to guide algorithms for stage-specific treatment. The clinical staging system for GC is presented in Table 1-3.

The term early gastric cancer (EGC) has been widely used in recent decades as the interest in screening or surveillance for GC grew. EGC is designated for the GC lesions confined to mucosa and/or submucosa irrespective of lymph node involvement or tumor size. In light of the TNM system, EGC refers to any GC case with T1 primary tumor. In clinical classification system, EGC normally refers to all Stage 0 and Stage 1 patients and part of Stage 2 GC patients. Clinically, EGC is a strong indication of endoscopy-based procedures as the first-line treatment. The diagnosis of EGC envisions an excellent prognosis (5-year survival rate > 90%) in contrast to the poor survival of patients with advanced stages.

Table 1-3. Clinical staging system for gastric cancer

Stage		Tumour	Node	Metastasis
Stage 0		Tis	N0	M0
Stage 1	IA	T1	N0	M0
	IB	T2	N0	M0
		T1	N1	M0
Stage 2	IIA	T3	N0	M0
		T2	N1	M0
		T1	N2	M0
	IIB	T4a	N0	M0
		T3	N1	M0
		T2	N2	M0
		T1	N3	M0
Stage 3	IIIA	T4a	N1	M0
		T3	N2	M0
		T2	N3	M0
	IIIB	T4b	N0	M0
		T4b	N1	M0
		T4a	N2	M0
		T3	N3	M0
	IIIC	T4b	N2	M0
		T4b	N3	M0
		T4a	N3	M0
Stage 4	IV	Any T	Any N	M1

(Washington 2010)

1.1.2.3 Lauren system for gastric cancer

Another simple but well accepted classification system is called Lauren system, which is specifically designed for gastric adenocarcinoma (Lauren 1965). Based on the histological status of gastric mucosa, the Lauren system categorizes GC into intestinal type, diffuse types and mixed type. The intestinal type of GC is called “epidemic” type owing to the fact that it arises from the gastric mucosa and retains glandular structure and cellular polarity. This type has been the main histological form of

GC in the world (Bertuccio et al. 2009). The diffuse type of GC disease differs in two important aspects from the intestinal type. It shows an invasive growth pattern and is thought to be closely related to genetic polymorphism. The diffuse type accounts for a small percentage of GC cases (Bertuccio et al. 2009; Singapore Cancer Registry 2011). Therefore, this thesis took intestinal type to illustrate the benefit of preventive programs.

1.2 Global Burden of Gastric Cancer

GC remains a global public health concern. Every year, there are around one million GC cases and 700,000 GC related deaths , which account for 8% of the total cancer cases and 10% of total cancer deaths in the world respectively (Jemal et al. 2011). With a fatality-to-case ratio of 70%, GC is a deadly disease making it the second most common cause of death due to cancer worldwide. Although more than 70% of incident cases occur in developing countries and 42% in China alone, age-standardized incidence are comparable between developed and developing countries.

1.2.1 Gastric cancer incidence

Recent decades have witnessed a substantial decrease of GC incidence in the world. The reasons are not yet clear. Data have shown that this decrease was driven by gastric carcinoma located in the distal stomach. Although it is believed that this declining trend will continue in the near future, it would not be able to reduce the GC burden. Instead, the overall GC number most likely would increase for several decades to come as a result of population growth and increased proportion of older people in most countries (Forman and Burley 2006).

There is considerable geographic variation in GC incidence across countries and within an area. The populations with age-standardized incidence greater than 20/100 000 are categorized as high risk. The

intermediate risk countries have an incidence between 11 and 20/100 000 inclusive. If age-standardized incidence is below 10/100 000 population, the country is categorized as with low GC risk (Ferlay J 2004). The high-risk areas include East Asia, Eastern Europe, and parts of Central and South America (Jemal et al. 2011), while GC risk is low in Southern Asia, North and East Africa, North America, Australia, and New Zealand (Figure 1-3).

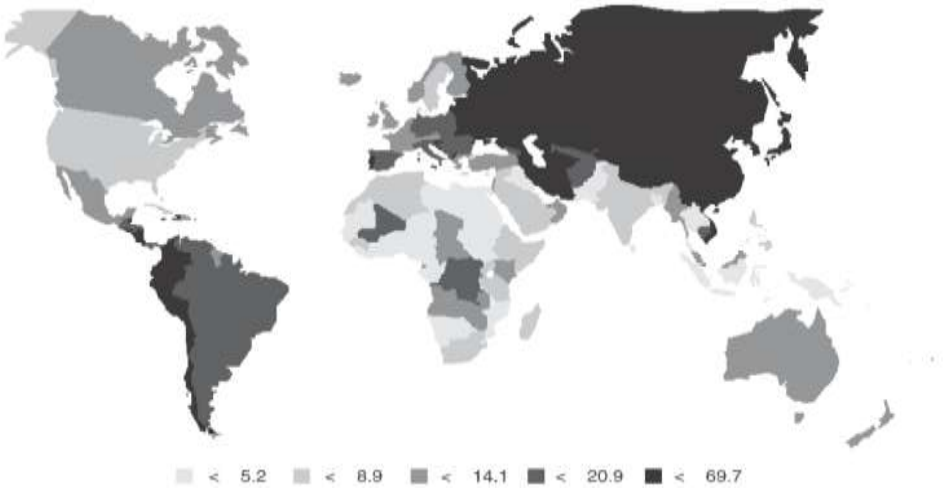


Figure 1-3: Geographic distribution of gastric cancer incidence rate

Unit: (1/100,000) (Forman and Burley 2006)

1.2.2 Gastric cancer mortality

Following the downward trend seen in incidence, GC mortality has also declined over time globally. The declining mortality has been attributed to the declining incidence as there has been no significant advance in GC treatment over the same period. Currently the prognosis of a GC patient is very poor. When gastric symptoms manifest, it is often too late for GC treatment to be effective.

Like incidence, the mortality of GC has strong geographical and ethnical characteristics. Age-standardized mortality is high in Asian countries. Korea and Japan have the highest GC specific mortality in the world. However, GC mortality is not directly associated with the level of economic development of a country. The stage-specific survival rates are similar in developing or developed economies.

Figure 1-4: Geographic distribution of gastric cancer mortality

Unit: 1/100,000 (Forman and Burley 2006)

1.3 Singapore Burden of Gastric Cancer

1.3.1 Gastric cancer incidence

Similar to the downward trend of GC incidences documented in other parts of the world, GC incidence declined steadily in Singapore with an average annual rate of 2.7% in males and 2.2% in females respectively. Now it ranks 5th and 8th among males and females in terms of cancer morbidity.

Singapore is a multi-racial society comprising Chinese, Malay and Indian. Chinese account for 91% of all GC cases diagnosed in 2003-2007. The GC risk for Malay males and Indian males are 32% (CI, 0.25 – 0.42) and 55% (CI, 0.33 - 0.89) of that for Chinese respectively. For females, age-standardized incidence for Malays and Indians are 37% (CI, 0.26-0.51) and 60% (CI, 0.42-0.86) of that for Chinese respectively. Basic GC statistics for Singaporean Chinese are presented in Table 1-4.

Table 1-4. Basic statistics of gastric cancer in Singaporean Chinese (2003 – 2007)

	Rank	Number	Crude Rate (1/100,000)	ASR* (1/100,000)	Percentage†
	Incidence				
Male	5	1235	19	16 .3	6.6
Female	7	811	12.2	8.1	4.1
	Mortality				
Male	4	927	10.8	9.8	7.9
Female	4	624	6.7	7.1	5.1

(Singapore Cancer Registry Committee 2010)

**ASR: age standardized rate.*

† Percentage of incidence and mortality of all cancers in Singapore

GC is associated with demographic variables. As shown in Figure 1-5, the GC risk of males doubles that of females; age is positively associated with GC risk and there is a sharp increase of GC incidence after 50 year old. Considering race, age and gender as indicators for susceptibility, elderly Chinese males are the most susceptible population for GC in Singapore.

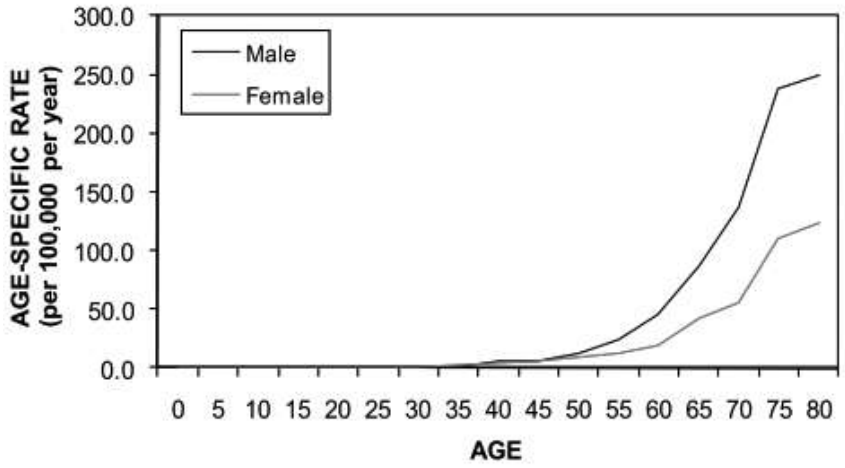


Figure 1-5. Age specific gastric cancer incidence by sex (2003-2007)

(Singapore Cancer Registry Committee 2012)

1.3.2 Gastric cancer mortality

The declining trend seen in the incidence was also observed in the GC mortality. Documented by Singapore Cancer Registry, the mortality has fallen by half to two-thirds over a period of 34 years for females and males alike. During the study period of 2003 – 2007, GC contributed 927 deaths and 624 deaths in male and female population respectively, the 4th ranking cancer related death for both genders in Singapore. The trends of GC mortality, incidences and relative survival were presented for both genders in Figure 1-6 and Figure 1-7.

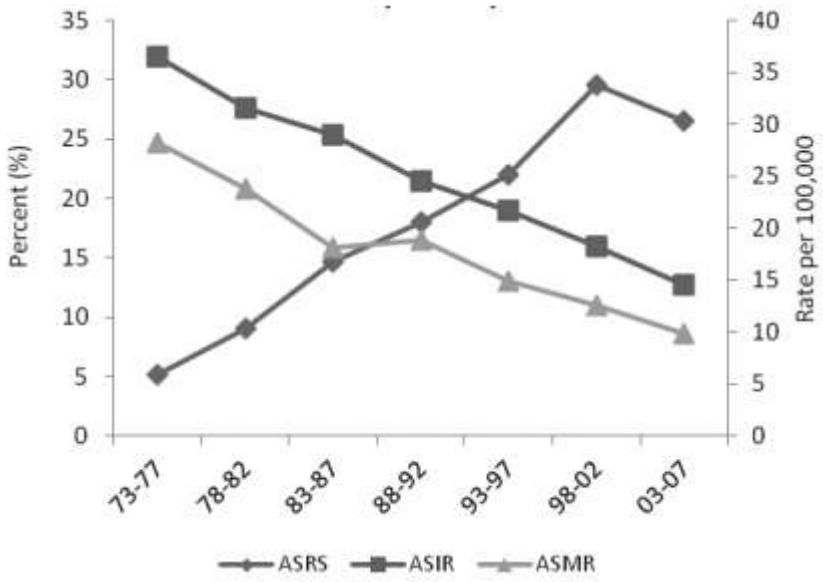


Figure 1-6. Declining trends in gastric cancer mortality and incidence for males

ASRS, age standardized relative survival; ASIR, age standardized incidence rate; ASMR, age standardized mortality rate

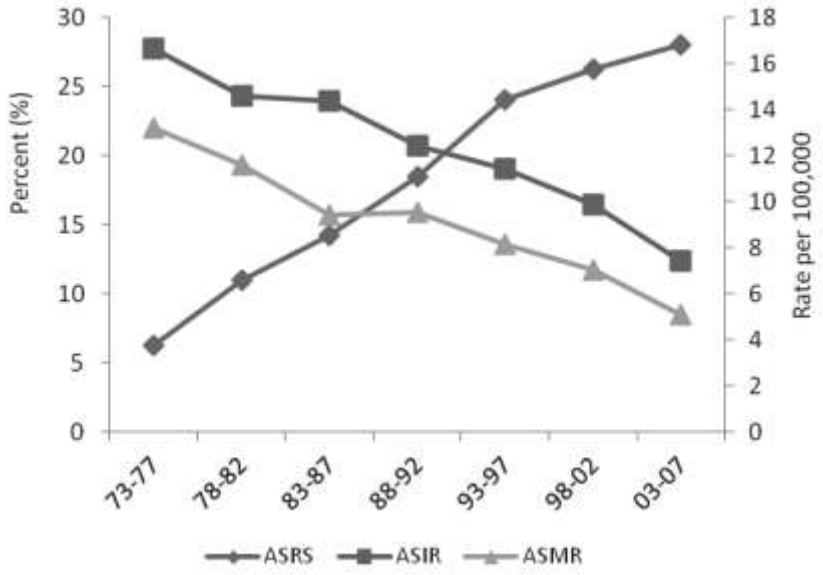


Figure 1-7. Declining trends in gastric cancer mortality and incidence for females

ASRS, age standardized relative survival; ASIR, age standardized incidence rate; ASMR, age standardized mortality rate

1.4 Risk Factors for Gastric Cancer Development

Helicobacter pylori (*H. pylori*), a common inhabitant of the human stomach, is the infective agent categorized by World Health Organization as class I carcinogen for GC development. *H. pylori* infection specifically increases distal GC in the antrum and body of the stomach where the vast majority of GC cases is diagnosed. GC in proximal stomach is not related to *H. pylori* infection. In a pooled analysis of 12 prospective studies, a six-fold increased GC risk was demonstrated (Helicobacter pylori and Cancer Collaborative Group 2001). *H. pylori* infection will be discussed further in Chapter II.

Dietary factors have long been proposed as important contributors to GC development and death. Dietary intake of salt, which was commonly used to preserve vegetables in Korea and Japan in old days, has been associated with increased GC incidence and GC mortality. Independent of other risk factors, salt intake is strongly correlated with GC specific mortality. The Pearson's correlation

coefficients were 0.7 in men and 0.74 in women both with statistical significance (P<0.001) (Joossens et al. 1996). Two studies conducted in Japan illustrated the elevated GC incidence in persons with excessive salt intake through pickled vegetables and salted fish (Shikata et al. 2006; Tsugane 2005).

In contrast to salt intake with food, a diet rich in fruit and vegetables was found to be protective from GC. A meta-analysis (Riboli and Norat 2003) and an observation study (Parkin et al. 2005) have proved that consumption of fresh fruits and vegetables would reduce GC risk with varying effects. A 44% reduction in GC incidence has been reported in another large prospective cohort study (Larsson,Bergkvist and Wolk 2006).

Smoking is an established causal factor for GC. A dose-response relationship of GC development to cigarette smoking was presented in an analysis by the European prospective investigation into cancer & nutrition study (Gonzalez et al. 2003). Smokers are 1.53 times more likely to develop GC (Ladeiras-Lopes et al. 2008) and 1.43 times more likely to die of it (Smyth et al. 2012). Alcohol use was only recently implicated to be a significant behavior factor for GC incidence (Tramacere et al. 2012).

Environmental factors also play an important role in GC development. Migration studies showed that first generation immigrants of high risk population still have higher risk than local population. The later generations, although sharing the same diet and behaviors, had a reduced risk at a level similar to the local residents (Kamineni et al. 1999).

Relatives of a GC patient have an increased risk of GC, which suggests the genetic mechanisms. A cohort of genes were identified capable of increasing human susceptibility to GC (Saeki et al. 2013). Germline mutations in MLH1 and MSH2 are confirmed with increased risk of intestinal

adenocarcinoma (Aarnio et al. 1997). Germline mutations in CDH1 will cause hereditary diffuse type of GC, which is characterized by early onset of the disease and may require prophylactic gastrectomy (Pharoah,Guilford and Caldas 2001). The mutation responsible for familial adenomatous polyposis is associated with antral adenocarcinoma in Japanese and Korean populations.

1.5 Clinical Management and Clinical Outcomes of Gastric Cancer

1.5.1 Gastric cancer treatment

GC management depends on the stage of the disease and general health of the patient. For cases in early stages (Stage 1 & 2) where the aim is a cure, surgery is the primary treatment modality with curative intent. The gastrectomy removes partial or entire stomach and the adjacent lymph nodes to achieve complete removal of the tumor tissues. For Stage 3 or Stage 4 cases, surgeries are used mostly to relieve symptoms, such as dysphasia and chronic pain. Patients operated for a curative intent accounts for only 30-50% of all clinical patients undergoing surgical procedures (Parkin,Pisani and Ferlay 1999).

Given the limit of the surgery, systemic treatment with adjuvant and neoadjuvant chemotherapy plays an important role. These drugs are effective in shrinking the tumor mass for better surgical outcome, decreasing the chance of recurrence, prolonging survival life and improving quality of life.

Recently, endoscopy-based procedures, namely, endoscopic mucosal resection and endoscopic submucosal dissection, have been developed and quickly spread around the world. These procedures are good alternatives to traditional open surgery for EGC. Studies have shown that these procedures achieve better clinical outcome for cases meeting specific criteria (Wang et al. 2012).

The GC treatment advances very fast. For the treatment of EGC, endoscopic mucosal resection and endoscopic submucosal dissection are widely used in Asian countries including Singapore (Ang, Khor and Gotoda 2010). Novel surgical procedures like sentinel node navigation surgery have started clinical applications in recent years (Wang et al. 2012). For advanced GC cases, systemic medical management remains the mainstay. Besides traditional chemotherapy, various immunotherapeutic strategies have been developed which include epithelial growth factor receptor inhibitor, T-cell-based antigastric cancer treatment, antiangiogenic agents, apoptosis promoters and specific immunotherapy (Amedei et al. 2011).

Despite these advances in GC treatment, stage-specific survival has remained steady for the past decade. The mortality reduction parallels the decline in incidence which strongly indicates a causal relationship. Early detection and early prevention, in comparison with treatment, should assume a bigger role for improved GC control in the future.

1.5.2 Clinical outcome 1 - survival rate

GC survival is stage-specific. There is a huge difference in outcomes between EGC and patients with advanced disease. The 5-year survival rate has achieved 90% for EGC in several populations (Lello, Furnes and Edna 2007; Tsubono et al. 2000), while it remains between 10 and 20% for Stage 4 GC patients (Lello, Furnes and Edna 2007). In Singapore, Koong et al reported 5-year survival rates of 90%, 70%, 40%, and 0% for Stage 1, Stage 2, Stage 3 and Stage 4 cases respectively (Koong et al. 1996). Singapore Cancer Registry data showed the distinctions of survival rates between local, regional and metastatic GC patients (Table 1-5). None of Stage 4 patients survived two years after diagnosis in Singapore.

Table 1-5. 5-year survival rates of Singapore Chinese (%) (1998-2002)

Age Group	Male		Female	
	Local	Regional	Local	Regional
50-64	64	8.6	75.6	22.5
65-74	47.8	11.7	44.3	8.6
75-	15.7	0	22.4	0

Recent years have witnessed great improvement in GC survival. In Singapore, the 5-year age standardized relative survival (ASRS) more than doubled in both males and females for the past 40 years. A similar trend was observed in other regions and populations (Bertuccio et al. 2009). Early detection of GC cases was speculated to be the major reason responsible for the survival improvement. The strongest evidence comes from Japan. It was reported that the national GC screening program detected most GC cases when they were still at early stage (Mizoue et al. 2003). As a result, the overall 5-year survival rate of Japanese patients is the highest in the world (Leung et al. 2008). Although Singapore has not established mass screening for GC, the rapid development in healthcare infrastructure offers easy access to endoscopic investigation, which has higher sensitivity and specificity than conventional approach in diagnosing the malignancy. Consequently, GC patients would be diagnosed in the earlier stages and receive curative treatment. Hence, the proportion of early GC patients has increased and at the same time, the 5-year survival rates have improved.

1.5.3 Clinical outcome 2 - quality of life

Quality of life (QoL), in addition to 5-year survival rate, has been advocated as another primary outcome for GC (Langenhoff et al. 2001). QoL measures the impact on the individual patients' perceived well-being due to disease and related treatment. In the case of GC, QoL has significant associations with clinical stage (Huang et al. 2007), type of surgery (Lawrence 2008), adjuvant therapy (Sadighi et al. 2006; Sadighi et al. 2009) and purpose of treatment (Sadighi et al. 2006; Sadighi et al. 2009). Thus, QoL score is very informative of the patient's situation and quality of care provided.

QoL can be measured by generic and condition specific QoL instruments. The results from generic QoL questionnaires can produce utility scores indicating the overall health status of a GC patient. These scores can be used for comparisons between GC patients and other disease groups. GC-specific instruments are designed to investigate detailed information specifically relevant to GC. Its scores are unique and therefore not appropriate for a cross-disease comparison. However, being more sensitive to changes due to the disease under investigation, GC-specific score is very useful to monitor disease progression or effect of treatment. Functional assessment of cancer therapy-gastric (FACT-Ga) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for stomach cancer are two commonly used disease specific QoL instruments in GC studies.

Assessment of QoL is also crucial for economic evaluation, particularly for cost-utility analysis. The validity of an economic model is greatly determined by its utility scores. Ideally, utility scores come from a QoL study of the target populations evaluated with a reliable instrument. Table 1-6 lists the utility scores used in cost-effectiveness analyses evaluating different GC screening strategies. Six of seven studies failed to show the instrument used to generate the utility scores. Therefore, the huge variation among the utility scores cannot be safely assumed to be the true QoL variation caused by the GC disease. This also makes one speculate that the reported cost-effectiveness may be the result of arbitrary selection of the utility scores.

Table 1-6. Utility of gastric cancer patients used in cost-effectiveness studies

Gastric Cancer Patient Type	Utility	Instrument	Reference
Advanced gastric cancer	0.797	EQ-5D	(Shiroiwa,Fukuda and Shimozuma 2011)
Gastric cancer	0.49	N/A	(Yeh,Ho and Hur 2010)
Gastric cancer	0.49	N/A	(Yeh et al. 2010)
Gastric cancer	0.5	N/A	(Xie et al. 2009)
Gastric cancer	0.55	N/A	(Rupnow et al. 2009)
Gastric cancer	0.38	N/A	(Xie et al. 2008)
Gastric cancer Stage 4	0.4	N/A	(Dan,So and Yeoh 2006)
Gastric cancer Stage 3	0.5	N/A	(Dan,So and Yeoh 2006)
Gastric cancer Stage 1 or 2	0.65	N/A	(Dan,So and Yeoh 2006)

CHAPTER II: GASTRIC CANCER PREVENTION

Given that the efficacy of GC treatment is not satisfactory, attention has been turned to the prevention of GC. Prevention strategies not only work towards the reduction in mortality, but in reducing GC incidence. With rapid growth of the understanding on natural history of GC development, there is a good theoretical basis on which preventive measures should be undertaken. The factors that support strategy for GC prevention include: (1) The main etiologic agent, *H. pylori* , is known to be amenable to drug therapy and has a low infection rate (Fendrick et al. 1999); (2) The decade-long precancerous stage allows adequate time for clinical tests to detect GC early (Watabe et al. 2005); (3) Host susceptibility genes that carry a high risk of the disease have been identified (Figueiredo et al. 2002); and (4) The framework has been clarified which proposes a multidisciplinary approach combining population screening with molecular biological techniques (Correa,Piazuelo and Camargo 2004).

2.1 Gastric Cancer Carcinogenesis

GC development is a multi-sequential and multi-factorial process which involves interactions between host factors, environmental factors and *H. pylori* infection (Figure 2-1). Correa's model was first proposed to describe the natural history of intestinal adenocarcinoma (Correa 1992). At present, the model is widely accepted and extensively consolidated by various studies. According to Correa's model (Figure 2-1), the onset of *H. pylori* infection triggers the cascade of GC lesions. Chronic *H. pylori* infection exposes stomach mucosa to long-term inflammation, which is referred to as chronic gastritis. If untreated, stomach mucosa will lose its normal structure of glands and then atrophic gastritis occurs. As atrophic gastritis progresses, gastric mucosa is replaced by bowel-mucosa-like epithelium called intestinal metaplasia. The severe and extensive intestinal metaplasia leads to dysplasia and subsequently to a neoplastic lesion. The progression from *H. pylori* infection to gastric

adenocarcinoma takes years or decades as independently estimated by two models (Liu et al. 2006; Yeh et al. 2008).

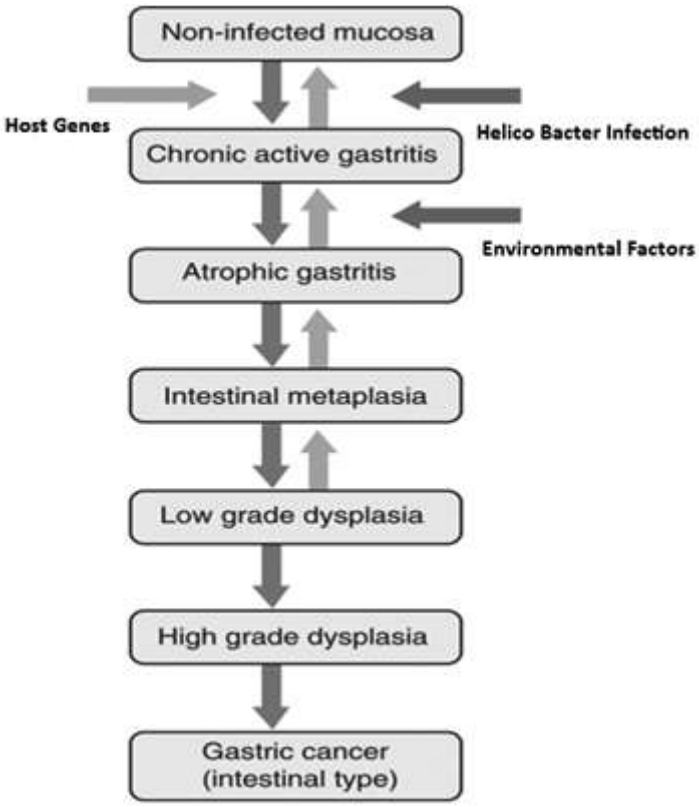


Figure 2-1. Carcinogenesis for Gastric Cancer

2.2 Chemoprevention- *H. pylori* Eradication

2.2.1 Consequence of *H. pylori* infection

Classified as a definite carcinogen for stomach cancer (de Vries,Haringsma and Kuipers 2007), *H. pylori* infection is viewed as a necessary but insufficient causal factor for non-cardia gastric adenocarcinoma (Fock et al. 2008). However, GC is one of a spectrum of end diseases caused by *H. pylori* (Figure 2-2). Approximately 1% of people infected with *H. pylori* will finally develop GC in their life time (Fock et al. 2009).

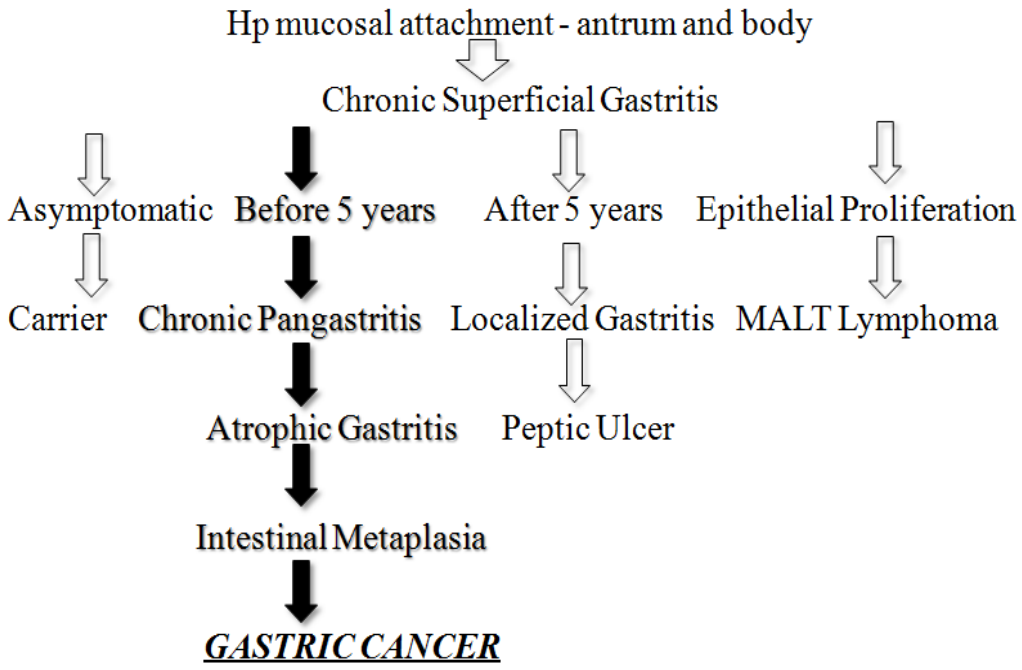


Figure 2-2. Clinical consequences of *H. pylori* infection

Given the role of *H. pylori* infection in GC development, intuitively, eradicating this infection would eliminate cancer risk before precancerous lesions develop. Therefore, screening for *H. pylori* and treating those with a positive finding is proposed as a population-based strategy in the prevention of GC.

2.2.2 Effectiveness and cost-effectiveness of *H. pylori* eradication

Many studies have been conducted to examine the effect on incidence and mortality from *H. pylori* screening and eradication. Observational studies in Asia found that *H. pylori* eradication significantly reduced the GC risk for patients with peptic ulcer disease (Mabe et al. 2009; Ogura et al. 2008; Wu et al. 2009) who are usually associated with higher GC risk.

For those with various precancerous lesions mentioned in the study by Correa et al, *H. pylori* treatment is effective in inhibiting their progression. One study reported that *H. pylori* eradication is beneficial in preventing the progression of preneoplastic lesions in the gastric mucosa (Sung et al. 2000). In a 6-year trial in Colombia, the combination of *H. pylori* treatment and dietary supplementation with antioxidants reduced the occurrence of gastric dysplasia (Correa et al. 2000). A 7.5-year clinical trial in China did not discover the preventive effect of *H. pylori* eradication for those already with atrophic gastritis. The researchers thus concluded that the *H. pylori* treatment can only be effective when administered early in the disease development. A meta-analysis of five randomized controlled trials derived a 35% reduction of GC risk for subjects infected with *H. pylori* (RR=0.65, 95% CI: 0.42–1.01) (Ford and Moayyedi 2009).

The cost-effectiveness of adopting *H. pylori* eradication is also demonstrated in multiple populations. *H. pylori* screening has shown to be potentially cost-effective in high-risk populations such as Japanese-Americans and Matsu residents in Taiwan (Lee et al. 2007; Parsonnet et al. 1996). A trial-based economic analysis demonstrated the cost-effectiveness of population screening for *H. pylori* infection in UK (Mason et al. 2002). In Singapore, Xie et al modeled one-time *H. pylori* screening in people 30 years or older (Xie et al. 2008). The study yielded an incremental cost-effectiveness ratio of $25,881 per QALY (quality adjusted life year) gained which is considered cost-effective for Singapore. Taking into account the pros and cons of *H. pylori* infection eradication, the Gastric Cancer Consensus Conference recommended that screening for *H. pylori* is appropriate for high risk

populations. However, for low or intermediate risk populations, its effectiveness is less clear (Talley,Fock and Moayyedi 2008).

2.2.3 Concerns about implementing population-based *H. pylori* screening

Although *H. pylori* screening sounds like a good candidate for GC control, there is so far no established national program completely based on *H. pylori* screening and eradication. Some researchers suggest the use of *H. pylori* test and serum pepsinogen as a stratification tool. However, its usefulness was questioned even for high risk population (Shimoyama et al. 2012). Firstly, the long-term efficacy of screening for *H. pylori* infection in the general population remains inconclusive. The benefit of *H. pylori* eradication for the subjects with precancerous lesions has not been firmly confirmed by randomized controlled trials (Liu et al. 2006; Wong et al. 2004). The proposed concept of "a point of no return" suggests that after certain point of GC development, regression to a less severe lesion is impossible. Secondly, a population-based program may be enormously costly and especially cumbersome for widespread implementation in developing countries (Ramsey 2007). Thirdly, as with the treatment of other infectious pathogens, drug resistance is a critical issue (Kwon et al. 2003). Furthermore, asymptomatic carriers of *H. pylori* are less receptive to the treatment. The possible adverse effects of treatment will result in reluctance to comply with therapy in this group. Besides wasting medical resources, low compliance potentially accelerates the emergence of drug resistance due to premature discontinuation of treatment. Lastly, there is evidence that that *H. pylori* eradication may increase the risk of other diseases such as gastroesophageal reflux (Blaser 1999).

2.3 Secondary Prevention – Gastric Cancer Screening or Surveillance

The 5-year survival rate of early stage GC is 95% (Isobe et al. 2011), whereas a Stage 4 GC patient has a low chance of surviving two years after diagnosis (Hosokawa et al. 2008; Koong et al. 1996). The great survival advantage of early GC cases supports the hypothesis that a patient's survival can be

prolonged if the disease is treated earlier. Therefore, secondary prevention focusing on early detection has assumed a paramount role in GC control worldwide.

2.3.1 Theoretical basis for secondary prevention of gastric cancer

Secondary prevention requires a long and identifiable preclinical phase where the abnormality can be examined by medical tests (Figure 2-3). A long preclinical phase is a necessary but insufficient condition for effective prevention. The following additional conditions need to be fulfilled:

1. Appropriate interventions are available and can have greater effect on clinical outcomes if applied earlier
2. All or most cases first go through a detectable preclinical phase
3. All or most cases in a preclinical phase progress to a clinical phase without intervention.
4. A good clinical test with high sensitivity and specificity is available and easily accessible

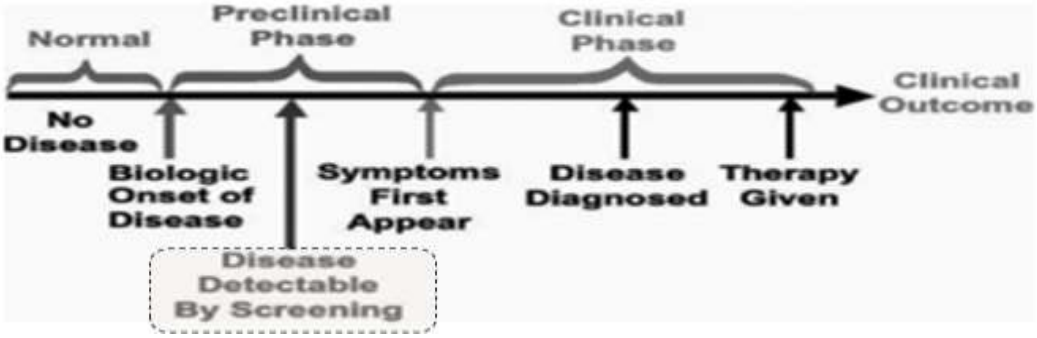


Figure 2-3. Natural history of a disease

Considering screening for GC, the above four requirements seems to be all fulfilled. This is demonstrated by the following evidence: (1) Correa's model has defined a years or decades long preclinical phase from chronic active gastritis to neoplastic lesion (Figure 2-1) (Liu et al. 2006; Yeh et al. 2008), (2) As the intermediate changes have been histologically characterized, they can be identified by endoscopic examinations with adequate accuracy, (3) Epidemiological data shows that

the majority of GC cases are adenocarcinoma that went through the pathway specified by Correa's model (Figure 2-1). (4) It is beyond controversy that regression of gastric precancerous lesions is unlikely. In summary, GC appears amenable to the secondary prevention to realize the survival benefit resulting from early detection.

2.3.2 Effectiveness and cost-effectiveness of gastric cancer screening or surveillance

Screening the general population has been very successful in reducing GC-specific mortality or improving survival time. Following the introduction of endoscopic screening, the age-adjusted GC mortality rates declined by 33% from 1.04 to 0.71 per 100,000 for males and by 60% from 1.54 to 0.62 per 100,000 for females in Japan (Matsumoto et al. 2007). In a historical cohort comprising 11,763 participants, subjects undergoing endoscopy screening had lower risk for GC death (relative risk = 0.35, 95% CI: 0.14-0.86) compared to those with no screening (Hosokawa et al. 2008). A 10-year follow-up study also reported a relative risk of 0.54 (95% CI: 0.38- 0.77) for GC death for subjects using screening service based on a population of 41,394 persons (Miyamoto et al. 2007). The down-stage effect by endoscopic screening was observed in Korea and Japan (Han et al. 2003; Kubota et al. 2000). From a perspective of resource allocation, cost-effectiveness was indicated for population-based screening in a Japan study (Tsuji et al. 1991). In Singapore, a decision-analytic model by Dan et al. recommended the 2-yearly endoscopy screening as a cost-effective strategy to prevent GC death in Singaporean Chinese men aged 50-70 years (Dan, So and Yeoh 2006).

Unlike screening which involves generally healthy subjects, surveillance focuses on the people with certain precancerous lesions and therefore at higher GC risk (de Vries,Haringsma and Kuipers 2007; Vannella et al. 2010). Multiple studies have provided evidence about the clinical benefit and cost-effectiveness of endoscopic surveillance in patients with atrophic gastritis, intestinal metaplasia, gastric ulcer or dysplasia (Dinis-Ribeiro et al. 2007; Hassan et al. 2010; Yeh,Ho and Hur 2010; Yeh et al. 2010).

Although a few clinical interventions have been tried and tested, scientific evidences support the use of endoscopy as the primary tool for screening or surveillance. Clinically, the sensitivity and specificity of endoscopy is higher than other interventions in diagnosing and staging GC (Voutilainen and Juhola 2005). As a screening tool, endoscopic examination has a detection ratio of 0.87%, approximately three to five times higher than photofluorography (Tashiro et al. 2006). It also achieved better cost-effectiveness in prolonging life expectancy in a Korean population (Chang et al. 2012). Endoscopy is also preferred over x-ray examinations as reported by a qualitative study (Choi et al. 2009).

2.3.3 Concerns about secondary prevention

Secondary prevention is associated with a few special biases. These biases are able to compromise the efficacy of a screening or surveillance program and waste medical resources. When designing and evaluating a healthcare program aiming for early detection, it is necessary to understand and prevent these biases.

Volunteer bias refers to the phenomenon that the participants in prevention programs tend to be healthier than the general population. This is a self-selection process whereby the people who are health-conscious tend to volunteer themselves for new medical services. The better survival of the screenees may solely be the fact that participants are generally healthier and have longer life expectancy. This bias will overestimate the survival benefit by screening.

Prognostic bias is another type of selection bias related to disease progression. A patient with slowly progressive disease is more likely to be detected than a fast progressive one as the long preclinical phase provides adequate time for clinical intervention. There is data to support the idea that a long clinical phase is associated with a long preclinical phase and verse versa. Therefore, those captured by

prevention programs have longer preclinical phase and naturally have better prognosis than the cases normally diagnosed. This bias also overestimates the effect of secondary prevention.

Lead time bias is defined as follows. A preventive test seems to diagnose the disease earlier in disease history, but there is no effect on the clinical outcome. It may appear that the intervention is very effective, when in fact it is the earlier diagnosis that artificially prolongs the survival time. Lead time bias will overestimate the survival time.

Over diagnosis bias has occurred when a screening program detects the silent cases which may never develop into a clinical case during the lifetime of a patient. It can also be caused by the eagerness to diagnose the target disease, which is commonly seen in the staff of a healthcare program. Those over-diagnosed cases are considered healthy under usual medical care thus would have better prognoses. This bias would cause overestimation of the effect of secondary prevention.

In the case of GC, few studies have been devoted to these negative aspects associated with GC screening or surveillance. Nevertheless some of them shed light on this area of GC prevention. Over-diagnosis was confirmed by a study in Japan (Hamashima et al. 2006) comparing observed and expected GC numbers detected by cancer screening. Lead-time bias could not be ruled out in the longer survival of asymptomatic groups undertaking GC surveillance in another study (Cardoso et al. 2012). Currently, there have been no large-scale studies to quantify the effect of lead time bias, prognostic bias, and volunteer bias and over diagnosis bias. An indirect way to estimate them is to use models simulating the natural history of GC (Liu et al. 2006; Yeh et al. 2008).

2.4 Existing National Screening Programs

GC screening remains controversial in most countries in the Asian-pacific region. Establishing a public health program on a national level is more than an epidemiological issue. Practical constraints are involved such as capacity of health care system, public perception and availability of medical services. Therefore, even in Asia where most countries are categorized as high risk for GC, only two countries (Japan and Korea) have national GC screening programs.

2.4.1 Japan

Japan has the oldest nationwide program for GC cancer screening since 1960s (Hisamichi 1989). Any individual older than 40 years is eligible for a yearly screening test. During inception of the program, double-contrast radiography was the primary tool followed by confirmative endoscopic procedures upon positive finding. With expanding access to endoscopy, endoscopy becomes the most popular screening modality.

The program in Japan has been successfully executed for half a century. Despite the seemingly low compliance rate of 20% or so (Graham and Asaka 2010), its effect is encouraging as shown by significant reduction in mortality and morbidity (Nakashima et al. 2010; Tanaka et al. 2011). Nowadays, the survival experience of Japanese GC patients is the best of the world. The majority of GC cases (90%) are at early stage with a probability of surviving 5 years after diagnosis (Davis et al. 2000). Japan is also interested in GC surveillance. A service structure based on hospital cancer registry is in the midst of completion (Graham and Asaka 2010).

2.4.2 South Korea

Korea started its National Cancer Screening program for GC in 1999. Like Japan, the Korean program targets people older than 40 years for a biennial screening arrangement. Two screening modalities,

direct upper-gastrointestinal series and endoscopy (or both), are available to be chosen according to the preference of participants. Given the relatively low cost and high specificity in diagnosing GC, endoscopy is the preferred method by the participants (Kim et al. 2011).

The program has been evaluated in several studies. It was found that the proportion of early gastric cancer identified is significantly higher in asymptomatic individuals undertaking endoscopy screening than in symptomatic individuals (Kim et al. 2000; Kong et al. 2004). Economic findings from two recent studies have confirmed the cost-effectiveness of this program (Chang et al. 2012; Cho et al. 2013).

2.5 Summary

Evidence so far supports that preventive measures are effective in reducing GC morbidity and mortality, despite concerns associated with both primary and secondary prevention. *H. pylori* eradication is unanimously recommended for asymptomatic persons of high risk populations. As for secondary prevention, consensus has yet to be reached regarding the adoption of GC screening and surveillance in a certain population or subgroup. However, it is clear that endoscopy is the best tool for such a purpose.

Singapore presently does not have a nation-wide health care program for GC control. However, with its advanced health care system and a small population, Singapore is an ideal place for implementation of such a program, which in turn calls for health services research to address practical issues such as cost of delivering clinical service, quality of life of GC patients and finally cost-effectiveness estimation. The population-based *H. pylori* infection and endoscopic screening have been evaluated by cost-effectiveness models (Dan, So and Yeoh 2006, Xie, Luo and Lee 2008). In terms of applicability of their findings, these two modeling studies are flawed by the common

weakness that the utility and cost were not generated based-on the target population that is Singapore Chinese. The surveillance strategy is yet to be evaluated or compared with recommended strategy. Under these circumstances, to obtain an informed choice of the optimal strategy for GC prevention and to facilitate implementation of an evidence-based national program in Singapore, we designed three studies, i.e. cost study, quality of life study and cost-effectiveness analysis. Hopefully, these three studies will provide useful suggestions for the decision-makers.

CHAPTER III: COST OF DELIVERING GASTRIC CANCER SURVEILLANCE

3.1 Background

In the global campaign to eradicate GC, which claims over 700,000 lives every year (Jemal et al. 2011), screening has assumed a paramount role but not without limitations (Leung et al. 2008). Even in Japan, the country with the highest incidence of GC, the cost-effectiveness of national GC screening is fading away due to the decrease in incident cases (Babazono and Hillman 1995). Considering the worldwide declining trend of GC incidence over the past two decades (Forman and Burley 2006), screening at the national level may no longer be the optimal strategy for GC eradication. Therefore, GC surveillance targeted at high risk subpopulations offers a complementary or alternative strategy given that hospital-based GC surveillance has already demonstrated its efficacy in detecting cases at early stages of cancer development (Dinis-Ribeiro et al. 2007; Whiting et al. 2002). It is also sensible for industrialized countries with very low overall GC incidence but containing specific ethnic groups such as Asian immigrants among whom GC remains a major disease burden (Cho et al. 2006; McCracken et al. 2007).

The Gastric Cancer Epidemiology Clinical and Genetic Program (GCEP) is an endoscopic surveillance program targeted at the Chinese population aged 50 years or above in Singapore, a country with an intermediate risk of GC (Fock and Ang 2010). The GCEP target population has a GC incidence much higher than the general population (Office 2008). Based on the preliminary explorations of GC endoscopic screening (Dan, So and Yeoh 2006), the GCEP was intended to inform the feasibility and benefit of GC surveillance as a control strategy for GC in Singapore. The GCEP system is established in four local general hospitals and has been running since 2004. Its surveillance follow-up is incorporated into the daily work routine of the participating hospitals.

Cancer prevention programs are costly undertakings and are featured by many years or even decades of time-lag between investment and the desired outcome. This then raises an important issue of cost efficiency - is the program producing the service at the least cost, i.e., the lowest price per unit of service? Cost efficiency is one of major determinants of actual cost-effectiveness delivered by a specific program (Bautista-Arredondo et al. 2008). However, to date, most cost analyses on cancer prevention have been cross-sectional studies which may have lead to skewed or biased cost estimates (Ekwueme et al. 2008; Jacobs and Baladi 1996; Smith and Barnett 2003). A survey-based top-down approach for data collection adopted in these studies is also prone to subjectivity (Mansley et al. 2002). The time-lag effect and long-term follow up associated with cancer prevention entails the understanding of continuous cost generation which a cross-sectional study is unable to address. Furthermore previous studies have not investigated the clinical cost, the patient personal cost and the program associated cost in the same study, and are thus limited in providing a more detailed and complete description of the broader economic impact of the program (Frew et al. 1999; Pavlik et al. 1995; Robert, Brown and Garvican 2000; Subramanian et al. 2011; Urban, Anderson and Peacock 1994).

With the above considerations, a trial program such as the GCEP is the ideal vehicle to empirically explore and evaluate the cost efficiency of GC surveillance. Evaluating the GCEP would be very informative for a future cost-effectiveness analysis of GC surveillance in Singapore and has direct relevance to government budgeting. This will prevent incomplete information from affecting optimal resource allocation decisions. Thus, we designed this study with the aims of: 1) informing resource allocation and program budgeting in the planning of national surveillance of GC in Singapore; 2) providing a comprehensive cost structure for full economic evaluation of GC surveillance both locally and worldwide; 3) elucidating the mechanisms underlying cost generation in cancer surveillance programs. This information will be of value to health administrators and planners in planning similar programs, as well as providing a framework for health policy researchers to undertake similar studies in different jurisdictions.

3.2 Methods

3.2.1 General approach

The GCEP is an ongoing trial surveillance program with the aim of eventually becoming a government-organized GC surveillance program. The most pertinent concern about establishing such a program is the financial impact on society by the program. Therefore, this study was conducted from a societal perspective, whereby the direct costs on GCEP (the healthcare provider) and the patients (the beneficiaries) in undertaking GCEP surveillance were measured by the bottom-up approach and reported as US dollars per person served (Johns, Baltussen and Hutubessy 2003).

3.2.2 Service mix of the GCEP program

According to the GCEP Protocol Version 7, once a subject was recruited, the 5-year annual follow-up would be customized to the individual's risk of developing GC assessed at baseline. Those fulfilling any of five criteria, namely: (1) dysplasia, (2) intestinal metaplasia, (3) atrophic gastritis, (4) GC family history, and (5) presence of *H. pylori* infection were categorized as high risk subjects and underwent annual oesophago-gastro-duodenoscopy (OGD) examination. All other subjects were classified as moderate risk and underwent OGD in Years 3 and 5 with telephone interviews or clinic visits in Years 1, 2, and 4. If patients were unable to be present for endoscopy, they were contacted by telephone for GC related symptoms. The primary outcome was the detection of early gastric cancer or high grade dysplasia.

3.2.3 Study site, period and sample

The GCEP consists of a decentralized service network involving the National University Hospital (NUH), Tan Tock Seng Hospital, Singapore General Hospital and Changi General Hospital in Singapore. This study used data from the NUH only, as it is a tertiary medical institution as well as

the program initiator. The GCEP can be divided into three distinctive phases : Start-up, Full-Implementation and Closeout (Johns,Baltussen and Hutubessy 2003), with each phase encompassing different activities (Figure 3-1). Compared to the Start-up and Closeout phases, the Full Implementation phase (01/04/2004 – 31/12/2010) captured most of the cost-intensive activities, and thus closely reflected cost generation assuming the GCEP was officially implemented on a national scale. Therefore this study chose the first 6.5 years from 01/04/2004 to 31/10/2010 of the Full Implementation phase as the costing period. To ensure a minimum 2-year follow-up, we concentrated our analysis on the subjects recruited between 01/04/2004 and 31/03/2008 (n=749) who are still under follow up. Thus we studied an open cohort from which a random sample of 216 cases (29%) was drawn through proportionate stratified sampling by age, gender and risk profile.

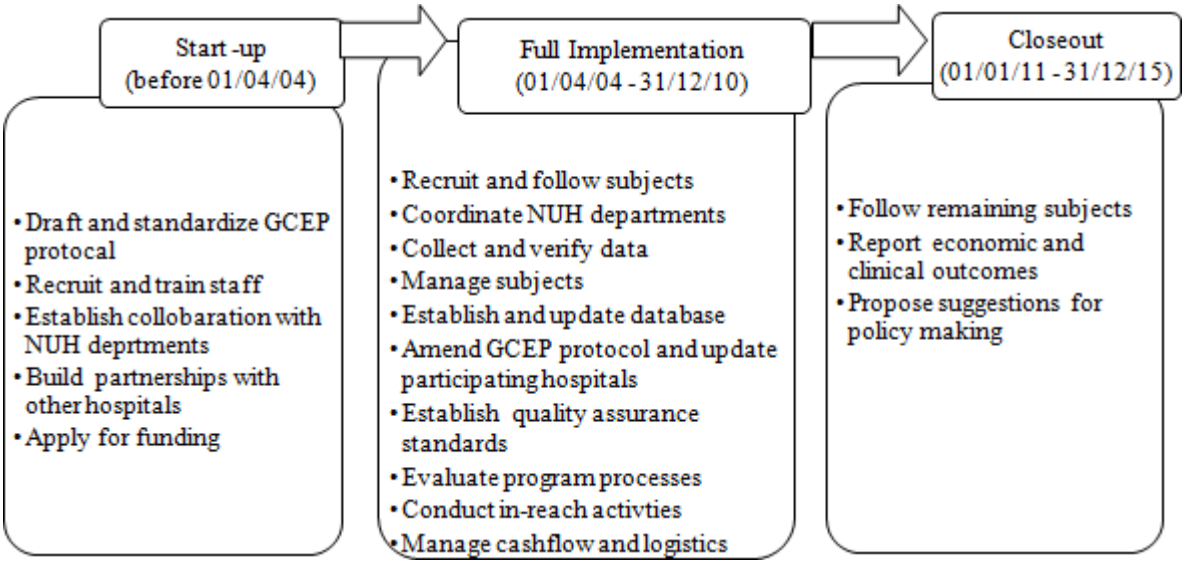


Figure 3-1: Phases and time frame of the GCEP

3.2.4 Resource quantification and costing

A task force funded solely by the GCEP grant was established at the NUH to exclusively operate the program. The GCEP as the service provider paid NUH for clinical, logistic and financial services. A co-payment system was also applied for clinical services whereby the GCEP provided free follow-up endoscopy, histology/biopsy and urease testing, and patients were liable for baseline endoscopy, medication, consultation and diagnostic tests prescribed at follow-ups (Figure 3-2).

From the NUH GCEP database, we retrospectively identified and quantified the resources consumed by a single subject at baseline and subsequent follow-ups by reviewing clinical casenotes and GCEP financial statements. Data sources of cost information included the Land Transportation Authority, Ministry of Manpower and the NUH financial office. The costs of each GCEP service were estimated by multiplying the quantities of various resources with the best-available unit cost for that resource. The cost components and estimation methods are summarized in Table 3-1.

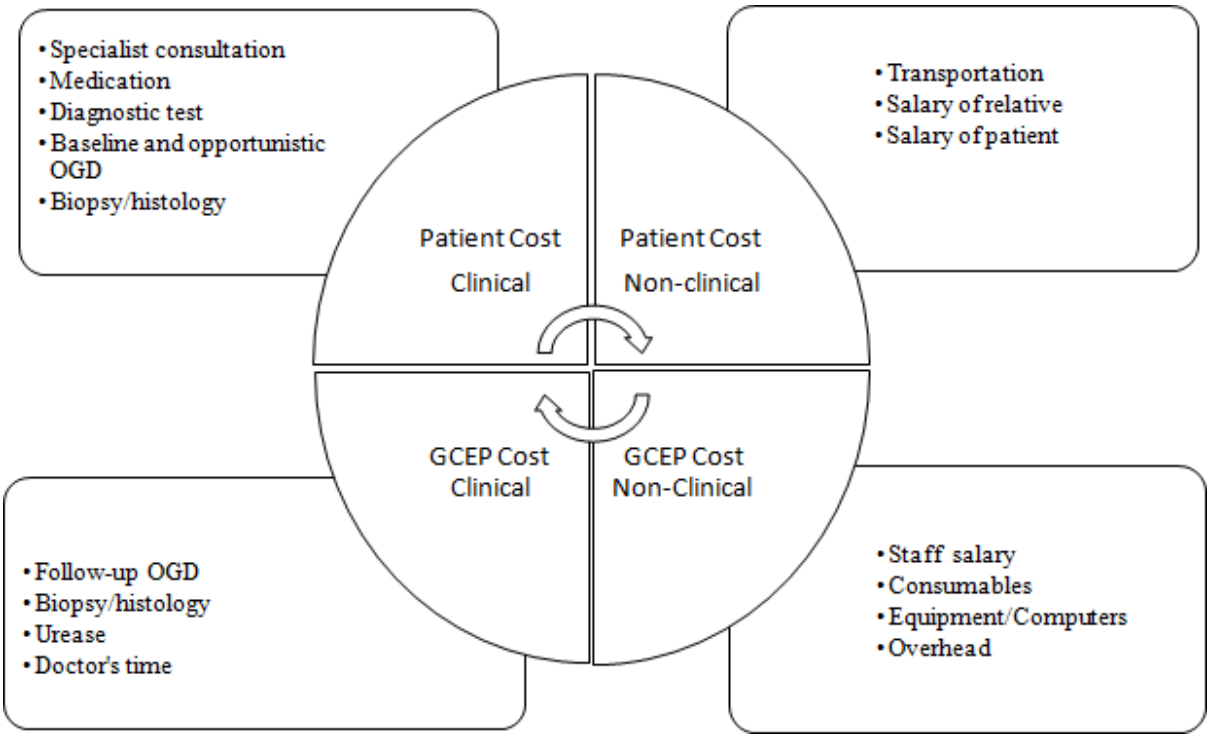


Figure 3-2. Cost Structure of the GCEP

Table 3-1. Cost components and cost estimation of the GCEP (2004-2010)

Components	Items	Estimate Methods	Data Source	Resource Quantification (per GCEP service)	*unit cost
Patient					
Clinical	Medications	Micro-costing	Casenotes & NUH	Name & dosage of medication	Price charged by NUH
	Consultation	Case-mix	Casenotes & NUH	Specialist consultation within 3 months after OGD	Mean charge by NUH
	Diagnostic test	Case-mix	Casenotes & NUH	Tests prescribed at follow-up	Mean charge by NUH
	Histology	Case-mix	Casenotes & NUH	Biopsy during OGD	Mean charge by NUH
	Endoscopy	Case-mix	Casenotes & NUH	Baseline & opportunistic OGD	Mean charge by NUH
	Transportation	National Mean	Casenotes & LTA	Round trip with mean mileage	Taxi fare based on mileage by year
Non-clinical	Patient time	Human capital approach	Casenotes & MOM	One day prescribed	Median age-gender specific wage by year
	Caregiver time	Human capital approach	Casenotes & MOM	One day prescribed	Median gross wage by year
GCEP					
Clinical	Endoscopy	Case-mix	Casenotes & NUH	Endoscopy & related procedure	Fixed charge negotiated with NUH
	Histology	Case-mix	Casenotes & NUH	Biopsy during OGD	Fixed charge negotiated with NUH
	Urease	Case-mix	Casenotes & NUH	Urease test during OGD	Fixed charge negotiated with NUH
	Doctor's time for OGD	Case-mix	Casenotes & NUH	Mean duration for OGD	Mean salary/minute
	Consumables	Direct allocation	Project record	Total spending/caseload	
	GCEP staff	Direct allocation	Project record	Total salary/caseload	
	Overhead	Direct allocation	Project record	Total spending/caseload	
Non-clinical	Capital	Direct amortization and allocation	Project record	Annual equivalent/caseload	

NUH, National University Hospital; OGD, oesophago-gastro-duodenoscopy; LTA, Land Transportation Authority; MOM, Ministry of Manpower

[*]Nine items used means, two items used medians, four items used direct allocation based on weight and yearly totals

As the study was conducted in 2010, the unit costs of clinical items were based on actual hospital charges at that time. Although hospital charges may not truly represent the cost of the services provided, these were the only data available. Considering that NUH is a not-for-profit public healthcare institution with most charges being set based on the principle of cost recovery, the use of charges in this instance would be a reasonable reflection of actual costs.

Non-clinical GCEP resources included capital, overhead costs, consumables and manpower, of which only yearly total expenditures were available. Equipment, particularly computers, was the major capital outlay for the GCEP. Therefore the 5-year useful life of a computer was used to calculate the annual equivalent of capital cost (WHO-CHOICE 2003). The overhead cost was a 20% increment of cash flow charged every year by the NUH to cover the office space, utilities, logistics and other services. The total amount of the GCEP staff salaries was used to estimate the cost of manpower. Unlike clinical resources, for which the consumption was recorded individually in the casenotes, non-clinical resources were shared by all the subjects served during a given period. Thus the cost of the non-clinical items, the so called 'program cost' were directly allocated to each subject (Johns,Baltussen and Hutubessy 2003; Subramanian et al. 2011). Given that the telephone interview, clinic visit and OGD examination consumed different amounts of time and non-clinical resources, they were assigned as '1', '2' and '3' unit weight respectively to reflect the relative utilization of these resources. The program cost was then assigned to each subject based on their individual weights. Caregiver time refers to when patients were accompanied by a person other than a nurse to the NUH.

3.2.5 Outcomes

All individual items were categorized into four components, from which primary outcomes originated for this study (Table 3-1). These outcomes comprised four cost indices that were informative and essential to future cost-effectiveness analysis and program budgeting (Drummond 2005). These indices (expressed as US$ per capita) were: 1) Overall Cost (which includes Patient Clinical, Patient

Non-clinical, GCEP Clinical and GCEP Non-clinical) quantifying the overall resource consumption; 2) Clinical Cost (which includes Patient Clinical and GCEP Clinical) quantifying the consumption of clinical resources; 3) GCEP Cost (which includes GCEP Clinical and GCEP Non-clinical) quantifying the economic burden on the health care provider – the GCEP; and 4) Personal Cost (which includes Patient Clinical and Patient Non-clinical) quantifying the cost for a subject to receive GCEP services. These cost indices were presented in 2004 US dollars with 3% discount rate (Weinstein et al. 1996).

3.2.6 Statistical analysis

All four cost indices were computed for each subject in every financial year within the costing period. The Student's t-test, Chi-Square test and survival analysis were used to compare continuous variables, categorical variables and rates between the sample and the cohort respectively. Since economic data are generally right-skewed and right-censored (Desgagne et al. 1998), this study used the semi-parametric bootstrapping method (n=1000) to calculate standard errors. The data in each year of the same subject was correlated across follow-up time. To adjust for this within-subject correlation, multivariate Generalized Estimation Equation (GEE) was used to model the data and to quantify and test the potential temporal trends in outcome indices. Due to the co-payment system, the temporal trends of the GCEP Cost and Personal Cost would be biased if baseline OGD was included in the analysis. Hence, we excluded the baseline data from the analysis of these two indices. As year 2004 had only baseline OGDs, the data from this year was not presented in the results of the GCEP Cost and Personal Cost. Statistical analyses were performed using SPSS (version 19; SPSS, Inc, Chicago, IL), STATA version 10 (Stata Corporation, TX) and Microsoft Excel 2007 (Microsoft, Redmond, WA). A p-value of 0.05 was used for significance for all statistical analyses.

3.3 Results

The workload of GCEP has been increasing throughout the costing period (Table 3-2).

Table 3-2. Yearly patient volume of GCEP (2004 to 2010)

Year	2004	2005	2006	2007	2008	2009	2010*	Total
New recruitments	121	164	121	305	343	179	104	1337
Follow-ups	5	141	326	475	762	1049	415	3173
Patients Served	126	305	447	780	1105	1228	519	4510

* *Costing period is up to 31/10/2010*

The study sample adequately represented the NUH GCEP cohort (Table 3-3). With the exception of the follow-up time, which was 2.5 months longer for the study sample (p=0.03), the sample and cohort were homogenous with respect to demographics, patient outcome and event rates with insignificant p values.

Table 3-3. Characteristics of the study cohort and sample

		Cohort* (n=749)	Sample* (n=216)	P
Age (year)		60.13 (7.32)	7.32 (60.23)	0.86†
Age group	50-59 years	426 (56.88)	121 (56.02)	
	≥60 years	323 (43.12)	95 (43.98)	0.88‡
Gender	Male	401 (53.54)	123 (56.94)	
	Female	348 (46.46)	93 (43.06)	0.39‡
Risk profile	Moderate	211 (28.17)	59 (27.31)	
	High	538 (71.83)	157 (72.69)	0.86‡
Follow-up (year)		3.34 (1.28)	3.55 (1.22)	0.03†
Outcome	EGC	6 (0.8)	1 (0.46)	
	Death	7 (0.93)	2 (0.93)	
	Drop-out	49 (6.54)	8 (3.70)	
	Survival	687 (91.73)	205 (94.91)	0.47‡
Incidence Rate‖		240 (108, 534)	131 (18, 930)	0.98§
Death Rate‖		280 (133, 587)	262 (66, 1048)	0.98§
Drop-out Rate‖		1959 (1481, 2592)	1049 (524, 2097)	0.83§

Abbreviation: EGC: early gastric cancer

[*] *Values are the mean (SD) for continuous variables and n (%) for categorical variables. Rates are reported with 95% confidence interval*
[†] *Student t-test*
[‡] *Chi-Square test*
[§] *Fisher's exact test based on rate difference*
[‖] *Unit of rates is 1/100,000 per year.*

The cost efficiency of the GCEP improved over time. As shown in 3, the monetary value of all four cost indices declined throughout the 6.5-year costing period. Despite variations over time, the downward trends of the cost indices were apparent from the onset of the GCEP. The mean Overall Cost of serving one subject steadily declined by 42.3% from US$1025 in 2004 to US$591 in 2010. The Clinical Cost, GCEP Cost, and Personal Cost also declined by 54.1%, 30% and 25.7% over this period respectively. The difference in magnitude of cost reduction is the result of the cost components constituting each index.

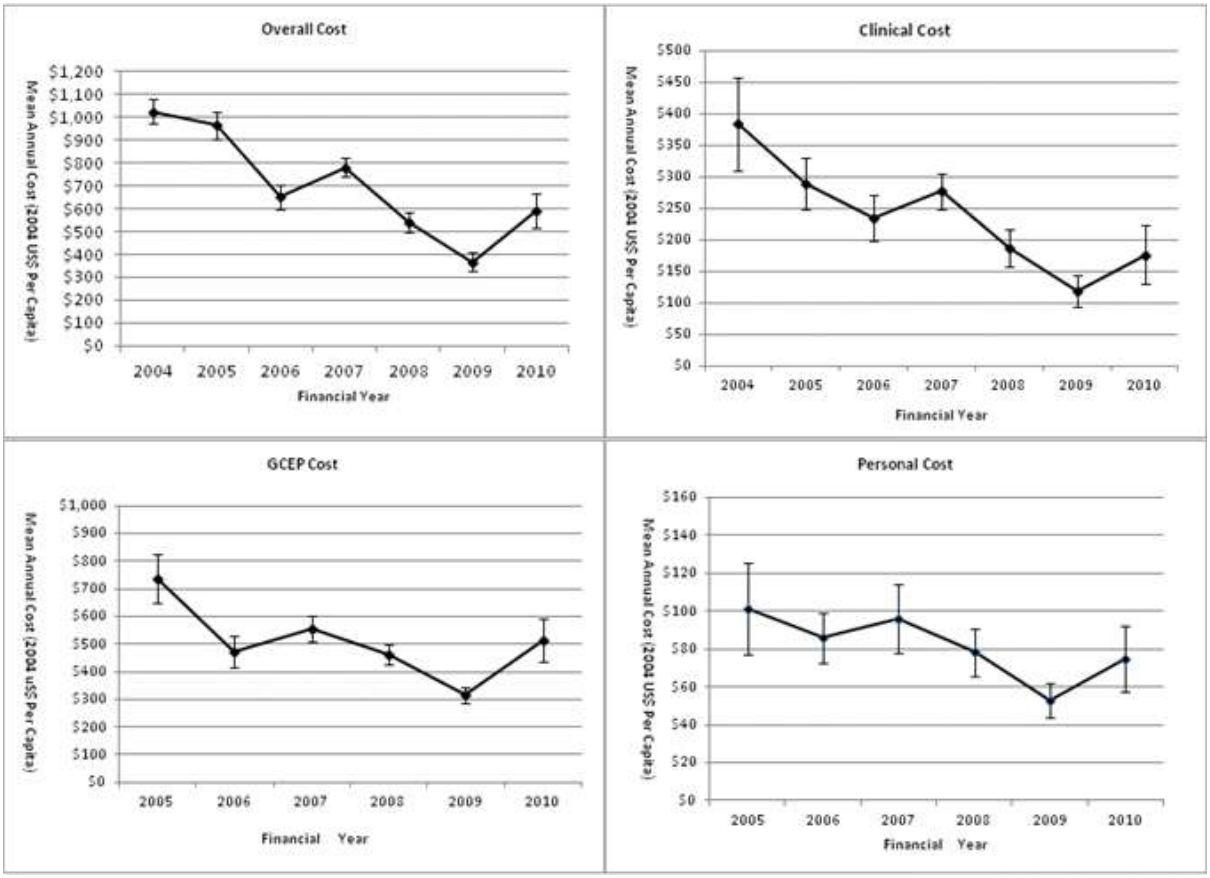


Figure 3-3. Temporal trends (2004-2010) of cost indices for the whole sample.

Individual points represent the means of cost indices in each follow-up year

As age and gender are critical for defining the target population for GC surveillance, the downward trends of the cost indices were further investigated in the age (50-59 year vs. ≥60 year) and gender (male vs. female) subgroups. In Figures 3-4 and 3-5, cost indices experienced slow and steady decline in all four demographic subgroups as they did in whole sample. Across the four groups, the Overall Cost dropped by between 40% and 47%. The Clinical Cost dropped by 52.1% to 58.4% and the GCEP Cost dropped by between 23% and 39%. The Personal Cost had the least percentage drop of 3.5% for the age group 50-59 years, and the biggest drop of 43% for the age group ≥60 years. The downward trends were demonstrated to be robust to age and gender. Furthermore, Figures 3-4 and 3-5 illustrated that the curves representing subgroups based on age or gender overlapped on large part and were almost identical, suggesting that resource consumption was not associated with a subject's age or gender.

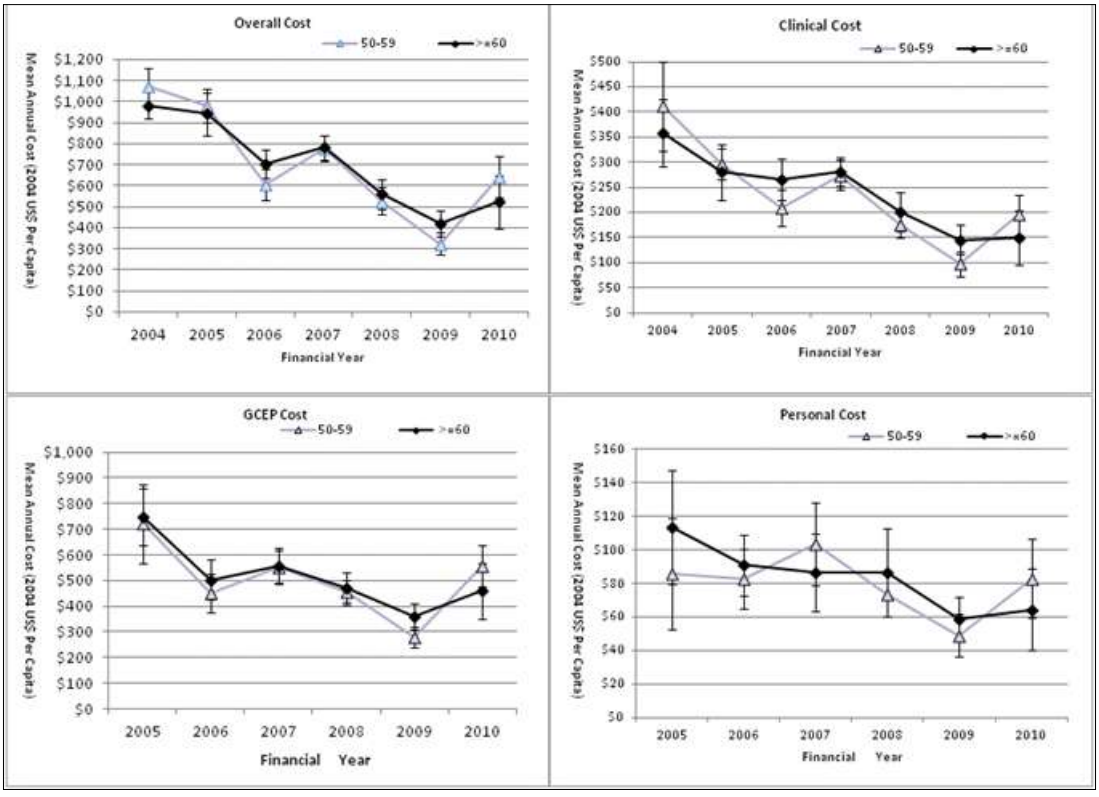


Figure 3-4. Temporal trends (2004-2010) of cost indices for the age subgroups.

Individual points represent the means of cost indices in each follow-up year

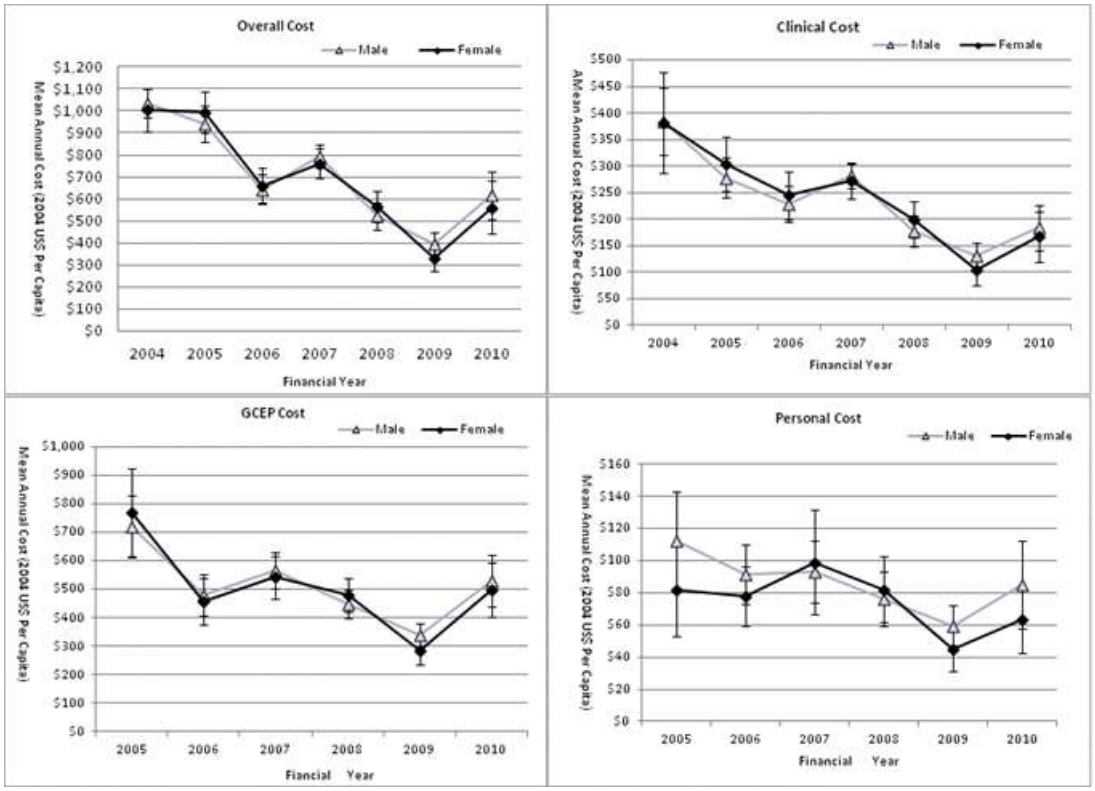


Figure 3-5. Temporal trends (2004-2010) of cost indices for the gender subgroups.

Individual points represent the means of cost indices in each follow-up year

As per the GCEP protocol, risk assessment at baseline determines the number of OGD which a GCEP subject will take during follow-up and is an important modifiable factor for resource allocation. As expected, the risk profile had a big impact on cost indices for the two risk groups. In Figure 3-6, the cost curves for the high risk group ran above those of the moderate risk group for all cost indices, illustrating that the high risk subjects consumed more resources than the moderate risk subjects. The Overall Cost, Clinical Cost, GCEP Cost and Personal Cost of the moderate risk group accounted for 77%, 68.1%, 60% and 65.1% of the high risk group respectively.

Risk profile also affected the downward trend pattern. The temporal trends were not universally downward for three pairs of risk groups or for all cost indices (6). The Overall Cost and Clinical Cost retained their downward trends for both the high risk and moderate risk groups. However, the GCEP Cost and Personal Cost differed dependent on the risk profile. On average, the GCEP Cost to serve one subject at the high risk dropped by 38.2%, while it increased by 62.6% for a moderate risk subject

over the costing period. Similarly, the Personal Cost paid by a single high risk subject dropped by 36.5%, while it increased by 76.1% from US$46 in 2005 to US$81 in 2010 in moderate risk subjects.

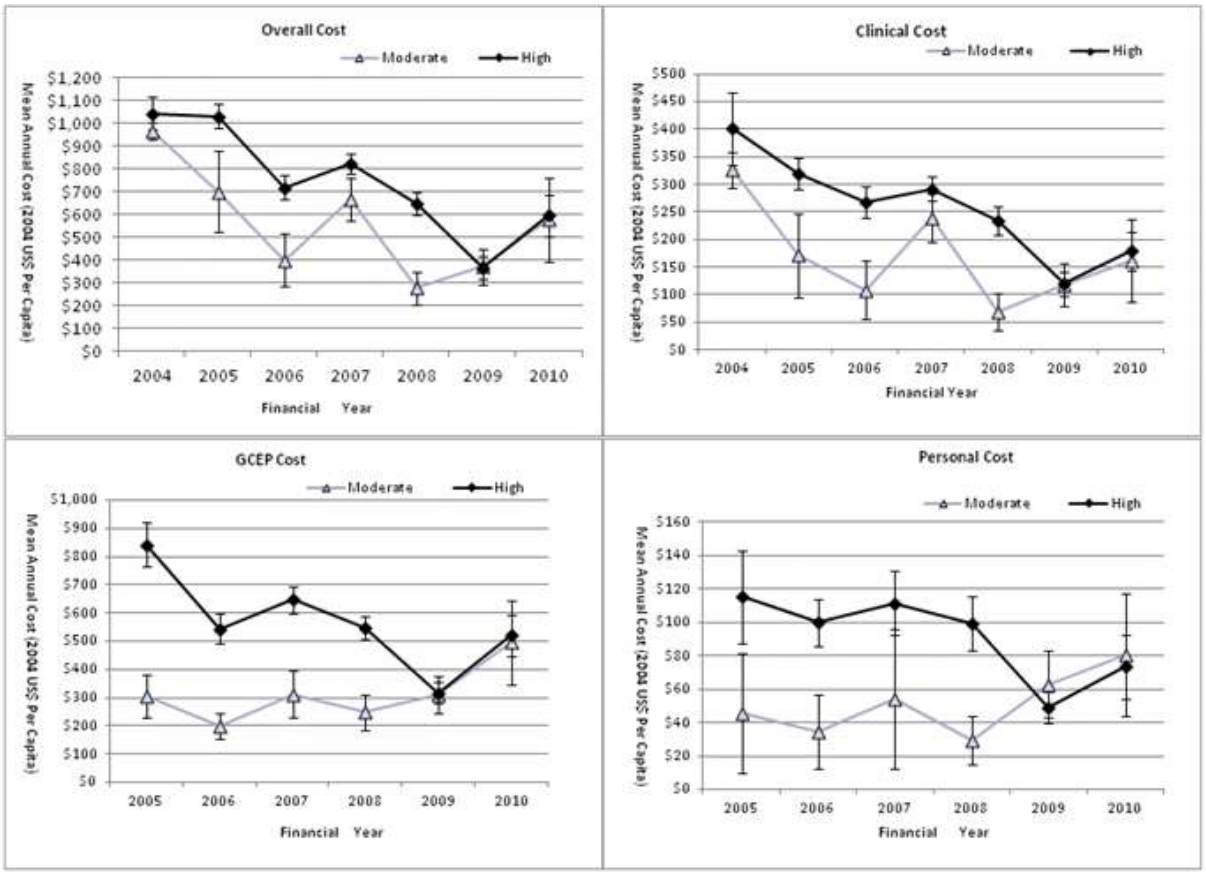


Figure 3-6. Temporal trends (2004-2010) of cost indices for the risk subgroups.

Individual points represent the means of cost indices in each follow-up year

The GEE models fitting the temporal trends of cost indices and the comparison of the trends between the three pairs of subgroups of age, gender and risk profile are presented in Table 3-4. Twenty six out of 28 GEE models in Table 3-4A confirmed the downward trends as shown in Figures 3-3 to Figure 3-6, with highly significant p values and negative annual change in monetary values. Only two GEE models fitting the GCEP Cost and Personal Cost for the moderate risk group suggested a cost increase over the follow-up period. Comparative analysis of the cost trends in the subgroups revealed how other factors affected resource allocation. Significant results were only found when more resources were allocated to the high risk group than to the moderate risk group (Table 3-4B). There were no significant differences in annual expenses within age or gender subgroups.

Table 3-4. GEE models fitting temporal trends of cost indices and comparison of subgroup trends.

		Overall Cost			Clinical Cost			GCEP Cost			Personal Cost		
		Mean	**95% CI**	**P**	**Mean**	**95% CI**	**P**	**Mean**	**95% CI‡**	**P**	**Mean**	**95% CI‡**	**P**
A: Temporal trends													
Whole Sample*		-106	(-117, -95)	<0.001	-40	(-46, -34)	<0.001	-48	(-63, -34)	<0.001	-9	(-12, -4)	<0.001
Age (year) *	50-59	-109	(-124, -94)	<0.001	-41	(-49, -33)	<0.001	-40	(-60, -19)	<0.001	-7	(-12, -1)	0.01
	>=60	-102	(-117, -87)	<0.001	-37	(-47, -28)	<0.001	-59	(-78, -39)	<0.001	-10	(-15, -5)	<0.001
Gender*	Male	-101	(-115, -87)	<0.001	-37	(-45, -29)	<0.001	-44	(-62, -26)	<0.001	-7	(-12, -1)	0.009
	Female	-112	(-131, -93)	<0.001	-43	(-53, -34)	<0.001	-54	(-77, -32)	<0.001	-10	(-15, -4)	0.001
Risk Profile*	High	-112	(-123, -100)	<0.001	-43	(-49, -36)	<0.001	-73	(-87, -60)	<0.001	-13	(-17, -10)	<0.001
	Moderate	-46	(-61, -32)	<0.001	-18	(-28, -7)	0.001	26	(3, 49)	0.027	5	(-3, 14)	0.212
B: Comparisons between subgroups													
>=60 year vs. 50-59†		21	(-23, 65)	0.36	17	(-5, 40)	0.127	34	(-17, 84)	0.188	4	(-11, 18)	0.634
Male vs. Female†		10	(-35, 54)	0.675	1	(-21, 22)	0.965	15	(-34, 65)	0.536	7	(-8, 21)	0.382
High vs. Moderate†		192	(155, 228)	<0.001	87	(68, 104)	<0.001	226	(190, 263)	<0.001	39	(26, 52)	<0.001

Abbreviations: C.I., confidence interval

**Means decrement/increment across costing period.*

† Means of differences between two subgroups across costing period

3.4 Discussions

To the best of our knowledge, studies about continuous cost generation of cancer prevention programs have not been previously reported despite that many studies have acknowledged the limitations of cross-sectional cost estimates. Our study attempts to fill this gap. The gradual and continuous decline of cost indices in our study strongly indicated the ever-improving cost efficiency of endoscopic surveillance for GC through the GCEP during the observation period. This study as a free standing cost analysis, despite its inability to compute the cost-effectiveness ratio, provided important empirical evidence for program management and ultimately for value-for-money decision making. Cost studies of long-term GC surveillance have long been anticipated worldwide given that research already illustrated the benefit of GC surveillance (Filomena et al. 2011; Whiting et al. 2002). Exploring the mechanisms underlying our results would be of universal interest to GC researchers.

Economy of scale is considered the main reason for the cost reduction, especially for the Overall Cost and the GCEP Cost (Mansley et al. 2002; Subramanian et al. 2011). Previous studies have shown that as screening volume increased, the average cost borne by the health care provider to serve one subject decreased, thereby approximating an inverse relationship (Breen and Brown 1994). The GCEP experienced a 7-fold increase of patient volume from 175 in 2004 to 1223 in 2009. Consequently the average cost decreased because fixed costs spread out horizontally across the number of subjects served every year and vertically along the implementation time. Correlation analysis showed a negative correlation coefficient between workload and Overall Cost and GCEP Cost, with the former achieving statistical significance ($r= -0.821$, $p=0.023$).

More efficient utilization of the resources within the GCEP system was another factor driving the GCEP Cost down. It is well known that public health programs improve operational efficiency through self-learning (Smith and Barnett 2003), which in return leads to decreased costs borne by the

service provider. Having been in operation for seven years and with quality assurance protocols in place, the GCEP could optimize work-flow processes by shortening waiting times, avoiding repetitions and enhancing service awareness in team members (Sickles et al. 1986). Although specific parameters were not set to gauge its work-flow processes, it was fair to assume that the self-learning mechanism took effect, especially in the inception of the Full Implementation phase which was the costing period of our study.

The decline in Clinical Cost indicated that subjects consumed less of the clinical services, which consist of follow-up OGD, specialist consultations, diagnostic tests and medications (Table 3-1). This is most likely due to a reduced demand for clinical services in later follow-ups when the subjects were experiencing fewer symptoms as a result of surveillance and associated treatment. Our findings were consistent with a cost study of a colorectal cancer screening program which showed that repeated screenings cost less than initial screenings because of the lower prevalence of disease in the rescreening group as opposed to first-time participants (Grazzini et al. 2008). Congruent with the previous observation, the Personal Cost also decreased as patients paid less for clinical services.

A further reason for the Personal Cost reduction was the declining price of patient time estimated by the human capital approach (Ekwueme et al. 2008), whereby the opportunity cost of taking one day off work for an OGD or clinic visit was measured as a single day's salary. In Singapore, there was a large decrease in salary from the age group 50-59 years to the age group 60 years or above (Ministry of Manpower 2010). As one of the GCEP inclusion criteria was being age 50 years old or above, we noted that during the observation period, 42 (19.4%) subjects underwent the age change from 50-59 years old to 60 years old and above.

Subgroup analysis was conducted to explore the cost generation in subgroups categorized by age and gender, which are relevant to the diagnostic yield of a screening program (Denis et al. 2007; Nakama

et al. 2001). Similar to the observation for the whole sample, both gender subgroups experienced significant annual decreases with bigger decrements in females for all the four cost indices (Table 3-3). As for impact of age, compared with subjects 60 years or older, subjects between 50 and 59 years had a larger decrement in Overall Cost and Clinical Cost, US$109 vs. US$102 and US$41 vs. US$37 respectively, and a smaller decrement in the GCEP Cost and Personal Cost, US$40 vs. US$59 and US$7 vs. US$10 respectively (Table 3-3). However, comparing the average costs of the subgroups for either variable failed to reveal significant differences, as illustrated by the overlapping curves in Figures III-4 and III-5. The cost efficiency in subgroups as described above was of great significance in advising resource distribution among these subgroups and in computing population specific cost-effectiveness ratios subsequently.

As the cost-effectiveness of screening is sensitive to disease incidence in target populations (Dan, So and Yeoh 2006; Di Giulio et al. 2009), the GCEP classified subjects into high and moderate risk of GC which subsequently determined the frequency of surveillance OGD. The temporal trends of cost indices were statistically different between high and moderate risk groups (6 and Table 3-3). The Overall Cost and the Clinical Cost for the high risk group had annual decrements 2.4 times lower than those for the moderate risk group. The GCEP Cost and Personal Cost showed a downward trend in the high risk group, while they both increased over time in the moderate group. The cost difference between high and moderate risk groups was arbitrary as OGD frequencies were decided beforehand, yet it has implications for funding and for evaluating the cost-effectiveness of a specific population.

Compared to other published cost-analyses of cancer screening programs, our study was unique in four ways, in that we: 1) analyzed long-term continuous cost generation; 2) collected individual-level data; 3) identified and quantified all possible resources; and 4) studied multiple indices simultaneously. The advantages of these are discussed as follows.

Given that long-term or life-long follow-up is required in a cancer surveillance program we studied a prospective cohort, the GCEP, with 6.5-year follow-up data and reported on the temporal trends of cost indices, in addition to the point estimates which are the sole outcomes in cross-sectional studies (Ekwueme et al. 2008; Subramanian et al. 2011). There is a high likelihood that point estimates are skewed or biased depending on the period chosen in a specific study (Jacobs and Baladi 1996; Subramanian et al. 2008). Program activities and patient volume varv greatly from year to year resulting in inflated/deflated point estimates (Ekwueme et al. 2008; Whynes and Nottingham 2004). Our study, rather than overestimating/underestimating the cost values, reported on the temporal variation of costs that can be used to predict the variability and the evolution of the cost - two aspects crucial for program budgeting.

Regarding the quality of data, our study collected individual-level data based on the NUH GCEP database. The quality of our data afforded statistical advantages over aggregate data analyzed in other studies (Ekwueme et al. 2008; Legood et al. 2005). Our individual-level data captured person-to-person and year-to-year variations which allowed us to estimate the means and confidence intervals from actual distributions and to apply GEE models, thereby enhancing the validity and reliability of our results.

In addition, we used patient casenotes and GCEP financial statements to identify clinical and non-clinical items directly associated with program operation. A bottom-up approach was adopted to quantify resources consumed and to estimate their monetary value (Johns,Baltussen and Hutubessy 2003; Walker 2001), thereby avoiding subjectivity or recall bias when data is collected through a survey-based top-down approach (Smith and Barnett 2003), and ensuing high accuracy and completeness of the data.

A major contribution of our study was that we simultaneously investigated multiple cost indices, each of which has been a focus in previous separate studies (Ekwueme et al. 2008; Ekwueme et al. 2008; Mansley et al. 2002; Secker-Walker et al. 1999). To our knowledge, no study has investigated these indices simultaneously in a single study thereby overlooking the fact that these costs accrued concurrently. Complete and accurate cost data are crucial to both an economic evaluation and program planning. Economic evaluations tend to underestimate the cost because of poor representation of personal costs and program costs (van Gils et al. 2010). The personal cost represents the financial commitment of a subject to participate in screening (Frew et al. 1999; Secker-Walker et al. 1999), so it is associated with subject compliance and program effectiveness (Heitman et al. 2008; Zapka et al. 1989). Our study found that patients paid at the most 18.2% of what was borne by the service provider (the GCEP) (Figure 3-3), suggesting that co-payment is a viable arrangement. Program cost measures the expenditure on non-clinical activities and represent the internal resource allocation within programs. A cost analysis of a colon cancer screening program demonstrated that non-clinical activities consumed more than 50% of the total budget (Subramanian et al. 2011), exceeding the US federal standard of 40% (Centers for Disease Control and Prevention 2005). In our study, the Clinical Cost accounted for only 17.35% to 35.76% of the Overall Cost, (i.e., the non-clinical cost ranged between 64.24% and 82.65%) (3). Although this study took a societal perspective and applied a narrower definition of clinical service, as an organized surveillance program in a small country such as Singapore, a high proportion of non-clinical expenditure appealed to the more efficient internal resource allocation.

We acknowledge several limitations with our study. As a pure cost analysis, this study is inherently unable to inform the value-for-money decision which is of utmost importance. In addition, service underutilization which is negatively associated with program effectiveness, cannot be ruled out as a mechanism driving down the clinical and personal cost in our study. The co-payment system whereby patients commit to a certain amount of money could impede some patients from using GCEP services, especially those from low-income families (Heitman et al. 2008; McAlearney et al. 2007; Urban,

Anderson and Peacock 1994). Removal of patient costs has been demonstrated to increase the screening compliance (Baron et al. 2008). Retrospective data collection in the current study cannot accurately match the cost with the specific clinical or administrative activities. Therefore, we could not identify the area of inefficiency. As for the Personal Cost, we may have omitted some elements which could only be retrieved through personal interview. Furthermore, caution is needed to extrapolate the downward trends beyond the observation period, because all the factors accounting for the cost reduction have limits (Subramanian et al. 2011). Nonetheless, our results confirmed continuous cost decrements in the early phase after full implementation. However, data seemed to indicate that the descending momentum stopped in 2009 (Figure 3-3, Figure 3-4, Figure 3-5 and Figure 3-6). The ideal situation is that a program achieves its optimal cost efficiency and functions on its minimum average cost curve (Mansley et al. 2002). A measure of the success of a program is how soon this point is reached, however this was not captured in our study.

3.5 Conclusion

Our study highlighted the importance of assessing the cost efficiency of a pilot project for future economic evaluation and government planning. The downward trends in cost indices and the factors contributing towards them offers valuable insights for future program budgeting and policy making. It is crucial for health administrators and planners to identify these factors and to further maximize their effect on cost efficiency in order for their programs to succeed. Furthermore, our study illustrated the distinct pattern of resource consumption and its temporal variation in individual subgroups classified by variables defining the target population. These findings call for accurate classification of the target population and for the computation of a population specific cost-effectiveness ratio.

CHAPTER IV: QUALITY OF LIFE OF PATIENTS WITH GASTRIC CANCER

4.1 Introduction

Quality of life (QoL) has been increasingly recognized as an important outcome for cancer therapy (Conroy,Uwer and Deblock 2007). QoL assessment has special clinical significance in the management of patients with GC, as the malignancy in a large proportion of GC patients is manifested in the form of ascites or lymphangitis carcinomatosa, thus rendering the ordinary response criteria such as tumor size less informative. A valid and reliable instrument is critical to obtain QoL data of both clinical and public health relevance (Holzner et al. 2001).

As most QoL questionnaires are developed in western countries, validating these questionnaires for use in other target populations becomes a necessary task for health outcomes researchers and clinical physicians alike. The Functional Assessment of Chronic Illness Therapy (FACIT) is a collection of questionnaires developed primarily for the QoL measurement for various cancers. FACIT has been established internationally as one of the reliable and valid QoL measurement systems in clinical oncology (Webster,Cella and Yost 2003). The core module of FACIT, the Functional Assessment of Cancer Therapy- General (FACT-G), has advantage over other cancer-generic QoL instruments in sample size requirements (Cheung et al. 2005). Simply adding cancer specific symptom items for a particular organ to FACT-G derives an organ-specific cancer QoL instrument, such as those for colon, lung and breast cancer (Webster, Cella and Yost 2003). These instruments have been validated and widely used in different populations internationally (Saitoh et al. 2007; Tong et al. 2009; Uwer et al. 2011).

However, the GC specific module based on FACT-G, the Functional Assessment of Cancer Therapy-Gastric (FACT-Ga) (S. L. Eremenco 2004), has not been sufficiently validated. There are only two

recent publications validating FACT-Ga in Western populations (Debb et al. 2011; Garland et al. 2011), however there is no data for Chinese populations, which have a higher GC incidence and mortality (Ang et al. 2005; Bertuccio et al. 2009) observed not only in mainland China, but also ethnic Chinese communities residing in other countries such as Australia (Anikeeva et al. 2012; Zhang, MacLennan and Berry 1984).

Previous attempts have been made to validate FACT-G for its use in cancer patients of Chinese ethnicity (Cheung et al. 2009; Cheung et al. 2004; Yu et al. 2000) but GC was not covered explicitly in these studies. Therefore, how well the FACT-G or FACT-Ga performs in measuring the QoL of Chinese patients with GC remains unknown. In Singapore, the Chinese constitute 75% of the entire population and carries an intermediate risk of GC in general and a high risk in males aged 50 years or older (Fock and Ang 2010). Furthermore, the multilingual culture in Singapore enables the validation of both the English and Chinese versions of the instrument and its use in a broader population base. As such, we designed this study to examine the psychometric properties of FACT-Ga with a sample of GC patients from the Singapore Chinese population. Our aim was to validate FACT-Ga as a GC specific QoL instrument for use in Chinese populations. Empirical evidence of the reliability, construct validity and sensitivity to patients' clinical status of FACT-Ga is reported.

4.2 Method and Materials

4.2.1 Study sample

4.2.1.1 Sample size estimation

Guidelines of sample size requirement specifically for validation study are not available in the literature. For the FACIT questionnaires, a sample of 50 cancer patients are considered acceptable and adequate (Webster,Cella and Yost 2003).

4.2.1.2 Requirement of clinical heterogeneity

In order for an instrument to be used in various patient subgroups, questionnaire validation requires a sample of high clinical heterogeneity (Peter M. Fayers 2007), that is, the sample should be representative of all clinical cases commonly seen in clinical practice. It does not necessarily mean a complete list of clinical cases. However, for the factors of important clinical relevance, their variants should be present in the sample. The sufficiency of sample heterogeneity refers to the maximum coverage of clinical characteristics. In the case of gastric cancer, these factors refer to purposes of treatment (Sadighi et al. 2009) and clinical stages (Huang et al. 2007).

4.2.1.3 Sampling protocol

The study was conducted between November 2010 and October 2011 at NUH, Singapore. Patients from the General Surgery Clinic and the Cancer Institute of Singapore at NUH were recruited using the following inclusion criteria, 1) Chinese ethnicity, 2) age 45 years or older, 3) histologically confirmed GC, 4) at least two weeks after operation, 5) no evidence of other concurrent severe medical conditions, and 6) able to complete the questionnaires independently (Figure 4 1). The study was approved by the Domain Specific Review Board of NUH. All participants provided written informed consent.

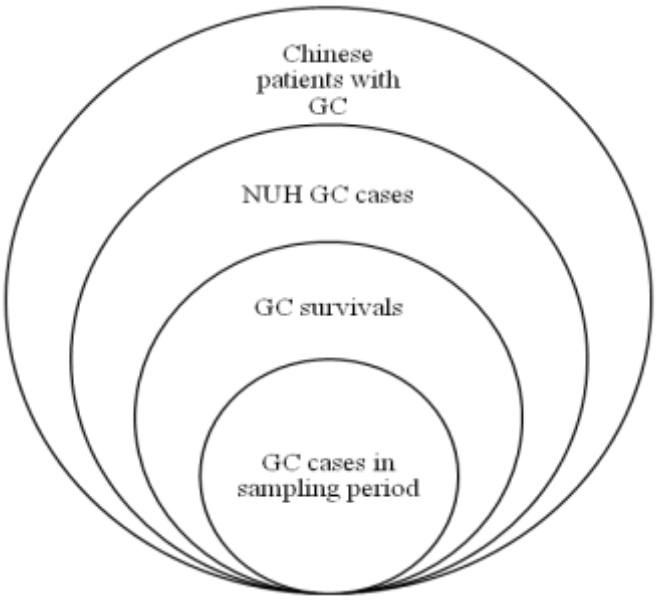


Figure 4-1. Sampling Frame of quality of life study

4.2.1.4 Patient recruitment

During the one year sampling period, 80 GC patients were approached. Among them, 75 agreed to participate in the present study, giving rise to a response rate of 94%. Three participants were illiterate and two participants had severe comorbidities. A further three patients suffered substantial missing information in their clinical data. So these eight patients were excluded. Finally, a sample of totally 67 GC patients was recruited into the study. The patient recruitment was illustrated in Figure 4-2.

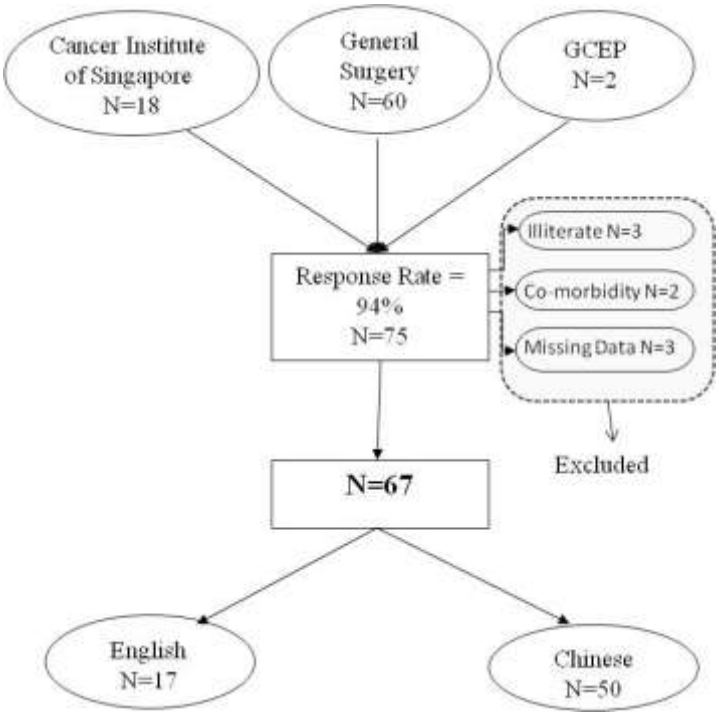


Figure 4-2. Subject recruitment process

4.2.2 Quality of life instruments

In the presence of the interviewer, patients independently completed two questionnaires, the FACT-Ga (Version 4) and the 3-level European Quality of Life-5 Dimensions (EQ-5D) in English or Chinese in accordance with their language preference. The order of the two instruments was randomized to rule out order effects (Cheung et al. 2004).

FACT-Ga evaluates the participant's life over the past seven days and consists of two parts: (A) the core module FACT-G which comprises four general subscales, namely physical well-being (PWB), social well-being (SWB), emotional well-being (EWB) and functional well-being (FWB); and (B) a 19-item gastric cancer subscale (GCS) surveying GC symptoms and adverse effects associated with GC treatment. The FACT-Ga items are rated on a 5-point Likert scale. Summation of item scores produces scores for the PWB, SWB, EWB, FWB and GCS subscales. The aggregate of the PWB,

SWB, EWB and FWB scores is the FACT-G total score. The FACT-Ga total score is the sum of the FACT-G total score and GCS subscale scores. Higher scores indicate a better quality of life.

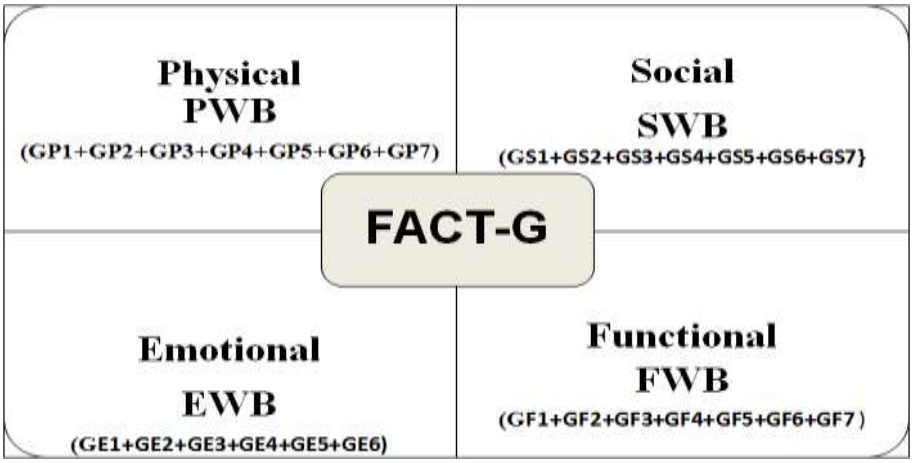


Figure 4-3. Factor structure of FACT-G

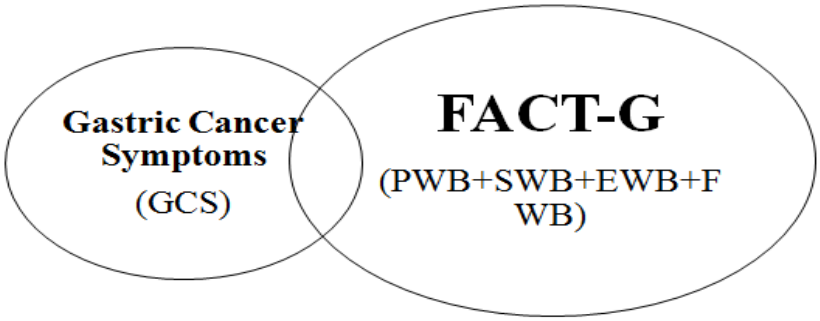


Figure 4-4. Factor structure of FACT-Ga

We chose EQ-5D questionnaire as the generic QoL instrument to validate FACT-Ga. Developed in the principle of time-trade-off, EQ-5D is a well-established instrument producing reliable QoL measures. The EQ-5D scores can be used as utility weight for calculation of quality adjusted life years in cost-effectiveness analysis. For the EQ-5D, participants were required to rate their QoL on the day of interview. The EQ-5D questionnaire measures five domains of the patient's life, i.e. Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression. The domain scores are used to compute a utility anchored between 0 (death) and 1 (full health) (Dolan and Gudex 1995). Similar to

FACT-Ga scores, higher EQ-5D utility indicates a better quality of life. The utility weight for each domain is presented in the Table 4-1. The EQ-5D utility is calculated by the formula below.

EQ-5D Utility = 1 - 0.081 – 0.269 (if any domain is rated at level 3)

- (β_M*Mobility + β_S*Self-care + β_U*Usual Activity + β_P*Pain/Discomfort + β_A*Anxiety/Depression)

Table 4-1. Utility weights for EQ-5D domains

	Constant 1	Constant 2	Mobility (β_M)	Self-care (β_S)	Usual Activity (β_U)	Pain/ Discomfort (β_P)	Anxiety/ Depression (β_A)
Level 1	0.081		0	0	0	0	0
Level 2			0.069	0.104	0.036	0.123	0.071
Level 3		0.269	0.314	0.214	0.094	0.386	0.236

4.2.3 Statistical analysis

The English and Chinese questionnaires were pooled for the analysis as the measurement equivalence between two language versions of EQ-5D and FACT-G has been previously confirmed in Singaporean Chinese (Cheung et al. 2004; Gao et al. 2009).

As participants were given the option of not answering the seventh item of the SWB subscale, GS7 (*"I am satisfied with my sex life")*, 32 (48%) participants did not respond to this item. The SWB subscale scores for these subjects were prorated following the FACIT Administration and Scoring Guidelines (Cella 1997). Ceiling effect for a scale is defined as percentage of subjects rating the highest scores. A percentage above 15% is considered unacceptable (Terwee et al. 2007).

Reliability was quantified as internal consistency by using the Cronbach's α. An alpha value equal to or greater than 0.70 was considered satisfactory (Nunnally 1978). The sensitivity to clinical severity was tested in relation to the clinical variables, Treatment Intent (curative vs. palliative) and Clinical Stage (6^{th} American Joint Committee on Cancer (AJCC) Stage 0,1,2,3 vs. AJCC Stage 4), using the effect size and the significance level of the Student's t-test.

Correlation analysis was performed to assess the construct validities of FACT-Ga. Convergent validity is supported if an item has a correlation coefficient of 0.4 or higher with its own scale (Peter M. Fayers 2007). Discriminant validity is supported if the correlation coefficient with its own scale is higher than that with any other scales.

The convergent and discriminant validities were further evaluated using the multitrait-multimethod (MTMM) approach for incomplete design, which explored all inter-scale correlations among the EQ-5D domains and FACT-Ga subscales (Trochim 2006). These correlations were quantified as Spearman correlation coefficients for rank data considering that three levels of each EQ-5D domain are not equally spaced (Salaffi et al. 2011; van Stel and Buskens 2006). Although it has been proposed to combine Level 2 and Level 3 as one category of "with problem" in correlation analysis with item levels (Luo et al. 2003), this study did not adopt this practice for the sake of loss of information.

As EQ-5D is a generic QoL instrument and FACT-Ga is a GC specific QoL instrument, there was no one-to-one correspondence of the QoL constructs across the two questionnaires. Based on content validity of two questionnaires, we hypothesized theoretically that the FACT-Ga PWB, EWB and FWB subscales corresponded to the EQ-5D Pain/Discomfort, Anxiety/Depression and Usual Activity domains respectively, whilst the FACT-Ga GCS subscale corresponded to the EQ-5D Pain/Discomfort domain. The correlations between these QoL construct pairs are the monotrait-multimethod correlations in the MTMM correlation matrix. As an incomplete design was adopted, these correlations would not line up as a validity diagonal. The remaining cross-instrument inter-scale correlations are termed multitrait-multimethod correlations. Both convergent validity and discriminant validity are supported if the strengths of the monotrait-multimethod correlations are stronger than the multitrait-multimethod correlations as expected *a priori*. The statistical software package SPSS v17 (SPSS Inc, Chicago, Illinois) was used to perform all analyses. A p-value less than 0.05 was considered statistically significant.

4.3 Results

The demographic and clinical characteristics of the sample are summarized in Table 4-2. The mean age of the participants was 67 years and the average survival time was 2.13 years after diagnosis. Approximately 75% of participants chose the Chinese version of the questionnaires. Our sample has a representative range of clinical cases, including patients diagnosed with AJCC stage 0 to stage 4, those with or without previous surgery, metastases, and a history of chemo/radiotherapy. The majority of these patients received treatment in hospital with a curative (71.6 %) rather than a palliative intent.

Table 4-2. Demographic and clinical characteristics of the sample

Variables	Categories	Value*
Age (years)		67.38 $\pm$ 11.87
Survival time (years)		2.13 $\pm$ 2.45
Gender	Male	43 (64.18)
	Female	24 (35.82)
Language	Chinese	50 (74.63)
	English	17 (25.37)
AJCC stage (6^{th} edition)	Stage 0	3 (4.48)
	Stage 1	19 (28.35)
	Stage 2	14 (20.90)
	Stage 3	13 (19.40)
	Stage 4	18 (26.87)
Metastasis	No	54 (80.59)
	Yes	13 (19.41)
Treatment Intent	Curative	48 (71.60)
	Palliative	19 (28.40)
History of surgery	Total gastrectomy	12 (17.91)
	Subtotal gastrectomy	37 (55.22)
	Surgical procedure	4 (5.97)
	No surgery	14 (20.90)
History of chemo/radiotherapy	No	44 (65.67)
	Yes	23 (34.33)

** Values are mean +SD for continuous variables and number (percent) for categorical variables.*

4.3.1 Ceiling effect and the reliability index

The distributions of the FACT-Ga scores and EQ-5D utility, the ceiling effect and the reliability index are presented in Table 4-3. Each score had a slightly left-skewed distribution as the medians were greater than the means. A floor effect was not observed but a ceiling effect was present for all scorers with notable values for the PWB (26.87%), SWB (16.42%) , EWB (16.42%) subscales and the EQ-5D utility (47.76%) (McHorney and Tarlov 1995). Cronbach's α values showed excellent reliability for both FACT-Ga and EQ-5D as only the EWB subscale had a value below 0.7 (Nunnally 1978).

Table 4-3: Score distributions, ceiling effect, reliability and item-scale convergence of the FACT-Ga and EQ-5D

	No of items	Possible range	Observed Range	Median	Mean ± SD	Ceiling Effect* (%)	Cronbach's α	Item-Scale Correlation (range)	No of success†/total (%)
PWB	7	(0 - 28)	(5 - 28)	26	24.31 ± 4.08	26.87	0.85	0.47-0.73	7/7 (100)
SWB†	7	(0 - 28)	(8 - 28)	23	21.51 ± 5.45	16.42	0.82	0.44-0.68	7/7 (100)
EWB	6	(0 - 24)	(10 - 24)	21	20.08 ± 3.40	16.42	0.62	0.08-0.56	4/6 (67)
FWB	7	(0 - 28)	(5 - 28)	21	19.29 ± 6.58	10.45	0.89	0.47-0.81	7/7 (100)
FACT-G	27	(0 - 108)	(47 - 108)	86	85.19 ± 14.55	2.99	0.89	0.08-0.81	25/27 (93)
GCS	19	(0 - 76)	(27 - 76)	63	59.91 ± 12.18	4.48	0.90	0.25-0.78	15/19 (79)
FACT-Ga	46	(0 - 184)	(74 - 184)	149	144.72 ± 24.51	2.99	0.93	0.08-0.81	40/46 (87)
EQ-5D	5	(-0.59 - 1)	(-0.06 - 1)	0.88	0.80 ± 0.28	47.76	0.81		

**Ceiling effect: Percentage of subjects who reached the highest score of the scale.*
†Cronbach's α was computed based on 6 items exclusive of GS7

Table 4-4. Sensitivity of FACT-Ga scores and EQ-5D utility to clinical severity

	Treatment Intent				Clinical Stage*			
	Curative (n=48)	Palliative (n=19)	Effect Size	P	Early stage (n=49)	Late stage (n=18)	Effect Size	P
	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)		
PWB	24.81 (3.90)	23.05 (4.36)	0.45	0.112	24.65 (4.01)	23.39 (4.24)	0.32	0.264
SWB	21.33 (5.86)	21.94 (4.34)	-0.10	0.686	20.94 (5.94)	23.06 (3.48)	-0.36	0.079
EWB	20.63 (2.95)	18.71 (4.11)	0.65	0.036	20.37 (2.97)	19.3 (4.38)	0.36	0.256
FWB	20.61 (6.26)	15.95 (6.31)	0.74	0.008	19.94 (6.52)	17.5 (6.57)	0.37	0.180
GCS	61.43 (11.59)	56.08 (13.12)	0.46	0.106	61.8 (10.95)	54.77 (14.12)	0.64	0.035
FACT-G	87.39 (13.77)	79.64 (15.34)	0.56	0.049	85.91 (14.57)	83.24 (14.74)	0.18	0.511
FACT-Ga	148.5 (22.76)	135.18 (6.77)	0.59	0.044	147.37 (22.99)	137.52 (27.67)	0.43	0.146
EQ-5D	0.86 (0.24)	0.65 (0.33)	0.89	0.016	0.84 (0.25)	0.68 (0.33)	0.66	0.031

**Early stage: AJCC stages 0-3; Late stage: AJCC stage 4*

4.3.2 Sensitivity

In the analysis of sensitivity (Table 4-4), the FACT-Ga QoL measures corresponded well with clinical severity as indicated by Treatment Intent and Clinical Stage. Patients treated with curative intent rated their QoL higher than those treated for palliation. Patients diagnosed with an early stage of GC (AJCC stages 0, 1, 2, 3) scored higher than patients diagnosed with the late stage of the disease (AJCC stage 4). These observations were in line with the direction of the overall QoL measured by the EQ-5D utility, which was significantly different between the subgroups of both clinical variables.

However, not all FACT-Ga scores showed statistical significance in the comparisons between clinical subgroups. The EWB and FWB subscales, FACT-G and FACT-Ga were significantly different between curative and palliative patients with a moderate effect size from 0.56 to 0.74 (D.Ellis 2010), while for the Clinical Stage, only the GCS subscale achieved statistical significance with an effect size of 0.64, and the SWB subscale achieved a borderline significance level of p=0.079.

Table 4-5. Multitrait-multimethod correlations matrix between EQ-5D domains and FACT-Ga subscales

	EQ-5D					FACT-Ga				
	Pain	**Anxiety**	**Usual Activities**	**Mobility**	**Self-care**	**PWB**	**EWB**	**FWB**	**GCS**	**SWB**
EQ-5D										
Pain/Discomfort	1									
Anxiety/Depression	0.52†	1								
Usual Activities	0.27*	0.37†	1							
Mobility	0.31*	0.44†	0.75†	1						
Self-care	0.25*	0.35†	0.66†	0.70†	1					
FACT-Ga										
PWB	**-0.66**†	-0.46†	-0.42†	-0.44†	-0.29*	1				
EWB	-0.46†	**-0.57**†	-0.48†	-0.45†	-0.25*	0.64†	1			
FWB	-0.39†	-0.52†	**-0.49**†	-0.58†	-0.45†	0.48†	0.60†	1		
GCS	**-0.63**†	-0.43†	-0.4†	-0.38†	-0.33†	0.80†	0.62†	0.48†	1	
SWB	-0.14	-0.38*	-0.2	-0.18	-0.2	0.13	0.30*	0.32†	0.13	1

Monotrait- multimethod correlations are highlighted in bold
** P<0.05*
† p<0.01

The construct validity of FACT-Ga was further evaluated in the MTMM analysis using EQ-5D (Table 4-5). Basically, the overall QoL quantified as the EQ-5D utility and as the FACT-Ga or FACT-G total score were strongly correlated (r = 0.70 and r = 0.66 respectively). The MTMM correlation matrix described in detail the inter-scale correlation patterns within either instrument, and more importantly across different instruments. The latter correlations connecting the EQ-5D domains with the FACT-Ga subscales were summarized in the lower-left square of the MTMM matrix called the Heteromethod Block. As hypothesized *a priori*, the four monotrait-multimethod correlations highlighted in Table 4-5 are generally higher than the multitrait-multimethod correlations. The correlation coefficients of the PWB subscale with the Pain/Discomfort domain (r = -0.66) and the EWB subscale with the Anxiety/Depression domain (r = -0.57) are the highest in their respective columns and rows. The correlation coefficient of GCS with the Pain/Discomfort domain (r = -0.63) is comparable to that of the PWB subscale. The correlation between the functional QoL constructs, the FWB subscale in FACT-Ga and the Usual Activity domain in EQ-5D was -0.49. Despite being the strongest correlation in the Usual Activity domain column, it is weaker than the two multitrait-multimethod correlations: the Anxiety/Depression domain with the FWB subscale (r = -0.52) and the Mobility domain with the FWB subscale (r = -0.58). As the FACT-Ga SWB subscale and EQ-5D Self-care domain are not conceptually related to any QoL construct of the other instrument, the correlations involving these two QoL constructs are the lowest of the respective rows or columns.

4.4 Discussion

Our study validated FACT-Ga in a heterogeneous sample of Singaporean Chinese patients with GC. The study sample covered the full spectrum of clinical cases which would allow for applying the validated questionnaire to various diagnostic groups. To the best of our knowledge, this is the first study dedicated to validating FACT-Ga for the Chinese as the target population. Both English and Chinese versions of the questionnaires were validated.

For this sample of outpatients, the measurement ability of the FACT-Ga appears to be limited in evaluating the QoL outcomes of patients who survived GC relatively well. The ceiling effect was observed for all scores, especially the PWB, SWB and EWB subscales, for which the percentage of patients rating themselves in perfect health exceeded a notable value of 15% (Table 4-3). The core module FACT-G also showed a ceiling effect when applied to other types of cancer patients from the same study population (Cheung et al. 2009). A ceiling effect above 15% could have a negative impact on other psychometric properties of an instrument (Terwee et al. 2007), for example, the sensitivity to change, as supported by the finding that FACT-G is weak in detecting the improvement in a patients' health status (Cheung et al. 2009; Garland et al. 2011)The evidence thus far seems to suggest that the existence of a ceiling effect of FACT-Ga compromises its potential as an evaluative QoL instrument.

The FACT-Ga questionnaire showed sensitivity to the clinical characteristics of different patient groups, supporting FACT-Ga as a discriminative QoL instrument. Treatment Intent and Clinical Stage are important concerns for doctors to consider when making a clinical decision. The QoL profile described by the FACT-Ga scores corresponded very well to the clinical classification by the two variables (Table 4-4). The patients in a more severe situation, i.e., those treated for palliation or those with the disease in the advanced stage rated their life worse. For either overall or specific QoL aspects, it is clear that the group differences are in the direction theoretically hypothesized and consistent with the findings from the EQ-5D.

Over and above its reflection of clinical severity of GC malignancy, the FACT-Ga scores exhibited differential sensitivity to clinical status. As suggested by the varying degree of the effect size and significance level of the t-test for each FACT-Ga score, the EWB and FWB subscales were sensitive to Treatment Intent, while the GCS and potentially the SWB subscales were sensitive to the patient's clinical stage (Table 4-4). Furthermore, the FACT-Ga instrument revealed an interesting finding about the social aspect of the patient's life, which was not measured in EQ-5D. The FACT-Ga SWB subscale scores were higher for severe cases than for less severe cases for both Treatment Intent and

Clinical Stage. This direction was opposite to that demonstrated by other scales. It would be too simplistic to ascribe the finding to random variation. We speculated instead that the Chinese culture played a part in this observation considering that our study population was Chinese. Sympathy is the essence of Chinese value systems and it could naturally be inferred that severe GC patients would receive more love and care from the people close to them. The SWB subscale is a measure of a patient's self-perception of family support and emotional closeness to friends. Therefore, the reverse trend of SWB scores is not unexpected and possibly culturally-specific.

In our study, the FACT-Ga instrument demonstrated excellent reliability in measuring the QoL of Chinese GC patients. Except for the EWB subscale, Cronach's α values indicated internal consistency reliability greater than 0.80 for the instrument and other subscales (Nunnally 1978). The EWB subscale had a Cronbach's α of 0.62, comparable to 0.60 as previously reported (Garland et al. 2011), yet below the generally accepted standard of 0.70 (Nunnally 1978). As the Cronbach's α of a scale is computed based on the inter-correlations among its constituent items, the extremely low item-to-scale correlation of the EWB subscale with its item GE2 (r = 0.08) was supposed to account for the suboptimal reliability of the EWB subscale (Ware and Gandek 1998). After excluding item GE2, the EWB subscale had an improved Cronbach's α of 0.72.

The Cronbach's α of the SWB subscale was reported as 0.82, indicating excellent reliability of the SWB subscale, based on the 67 participants who completed the first six items of the SWB subscale. The seventh item of the SWB subscale, GS7 asking about the sex life of the patient, introduced a non-response rate of 48% (n=32), which greatly reduced the sample size for computing the reliability index. The Cronbach's α would drop to 0.77 based on the 35 participants with complete information for seven SWB items. Non-response to the item GS7 was common in FACT-G validation studies in different cancer populations (Cheung, Daniel and Ng 2006; Fairclough and Cella 1996). Excluding GS7 in the calculation of Cronbach's α for the SWB subscale has been practiced to minimize the detriment of missing information (Cheung, Daniel and Ng 2006). Doing so also prevented an unstable

estimate of the reliability index due to an insufficient sample size, which was demonstrated by the Cronbach's α varying from 0.26 to 0.86 in five small samples (n=15) validating the FACT-Ga (Debb et al. 2011).

Construct validity of FACT-Ga was explored internally by examining the item-to-scale correlations for each item and externally by contrasting with EQ-5D. As hypothesized *a priori,* most items converged around their individual master subscales as required for good convergent validity. However, the Pearson correlation coefficient of item GE2 with the EWB subscale was only 0.08 with a 95% CI below 0.4. It was also associated with a definite scaling error implying that item GE2 should be included in the FWB subscale rather than the EWB subscale when FACT-Ga is used in Chinese GC patients (Ware and Gandek 1998). This finding supports the results of previous cross-cultural studies investigating the factor structure of the FACT-G in Asian populations (Fumimoto et al. 2001; Yu et al. 2000)

External validation involves a MTMM correlation matrix correlating the FACT-Ga subscales with the EQ-5D domains. The similar QoL constructs which were specified separately for EQ-5D and FACT-Ga yielded stronger monotrait-multimethod correlations than the multitrait-multimethod correlations in the Heteromethod block (Table 4-5). As shown by the monotrait-multimethod correlation coefficients, the PWB, EWB and GCS subscales are measuring the QoL aspects as intended. They are also able to discriminate the different aspects of a patient's life (Trochim 2006). With regard to a patient's functionality, the FACT-Ga FWB subscale was not strongly related to the Usual Activity domain of EQ-5D as we hypothesized, but to two EQ-5D domains, the Mobility and Anxiety/Depression domains, with similar strengths of correlation (r = -0.58 and r = 0.52 respectively). This may reflect the fact that the SWB subscale score is an integration of the mental and physical functions of a patient's life. The QoL constructs which are covered by only one questionnaire had the lowest cross-instrument correlations, for example, the SWB subscale of FACT-Ga and the

Self-care domain of EQ-5D. These results confirmed and substantiated the convergent and discriminant validities of FACT-Ga.

However, several limitations in this study must be noted. We were only able to recruit outpatients who usually have a better current QoL and prognosis than those hospitalized for radical treatments or bedridden at home. We acknowledge that the validity and reliability estimates were influenced by the narrow sampling due to logistical difficulties (Victorson et al. 2008). However, considering the statistical property of Cronbach's α and the correlations indicating construct validity, a more heterogeneous study sample generated by a wider patient pool would strengthen the current estimates (Peter M. Fayers 2007). With a cross-sectional sample, we were also unable to assess test-retest reliability and the responsiveness of FACT-Ga measures to QoL change over time.

4.5 Conclusion

Our study demonstrated that, when used in a Chinese population, FACT-Ga is able to detect group-differences in QoL outcomes between clinically distinct patient groups. The total and subscale scores from FACT-Ga can be considered reliable and valid measures of the QoL of Chinese patients with GC. This evidence supports the use of FACT-Ga as a discriminative QoL instrument alone or as a supplement to a generic QoL instrument in clinical trials and routine clinical practice.

CHAPTER V: COST EFFECTIVENESS ANALYSIS - MARKOV MODEL CONSTRUCTION

5.1 Gastric Cancer Prevention – From Mass Screening to Focused Surveillance

Mass screening for GC has shown to significantly improve patient survival (Hosokawa et al. 2008; Lee et al. 2006; Miyamoto et al. 2007). However, it is still hard to justify the establishment of population-based screening in a country with low or intermediate GC risk because of concerns about cost-effectiveness. Hence, cost-effectiveness evaluations of population-based screening are currently limited to jurisdictions with the highest GC incidences in the world, such as Japan, South Korea and Taiwan (Chang et al. 2012; Lee et al. 2007; Tsuji,Tsubono and Hisamichi 2001). Due to the dramatic impact of level of GC risk in a population on cost-effectiveness, the findings from these economic evaluations may not be generalizable to other populations.

Endoscopic surveillance, whereby patients with precancerous lesions are closely followed up for GC development by scheduled OGD examinations, has previously demonstrated the ability to detect GC at an earlier curable stage (Whiting et al. 2002). Multiple studies have provided evidence about the clinical benefit and cost-effectiveness of endoscopic surveillance in patient subgroups with atrophic gastritis, intestinal metaplasia, gastric ulcer or dysplasia (Dinis-Ribeiro et al. 2007; Hassan et al. 2010; Yeh,Ho and Hur 2010; Yeh et al. 2010). Thus, OGD-based surveillance is worthy of further investigation into its economic potential as a national strategy for GC prevention in countries at low to intermediate GC risk where mass screening is hardly warranted. The recommended OGD frequency for surveillance is once every year (Table 5-1).

In Singapore, the dominant Chinese population overall is at an intermediate risk for GC. The interest in early detection to improve the survival and quality of life of GC patients has stimulated a series of

endeavors. Based on decision-analytic models, Dan et al. reported that 2-yearly OGD screening is cost-effective in Singaporean Chinese men aged 50-70 years (Dan, So and Yeoh 2006); while Xie et al. evaluated the primary prevention strategy of Helicobacter Pylori screening and eradication in Singaporean Chinese aged 40 years or older (Xie et al. 2008). Additionally, an ongoing hospital-based demonstration project, GCEP (Zhu et al. 2009), was initiated in 2004 with the intention to provide empirical evidence on the feasibility and cost-effectiveness of endoscopic surveillance.

Table 5-1. Endoscopy frequency recommended for endoscopic surveillance for gastric cancer

Precancerous lesions	Surveillance	Reference
Mild atrophic gastritis	Annual OGD	(Graham and Asaka 2010)
Moderate or severe atrophic gastritis	Annual OGD	(El-Zimaity et al. 2001)
Intestinal metaplasia type II & III	Annual OGD	(Kapadia 2003)
Low grade dysplasia	Annual OGD	(Bustamante et al. 2002)
Gastric ulcer suspicious of cancer	Annual OGD	(Whiting et al. 2002)

However, consensus has yet to be reached regarding the optimal strategy for GC secondary prevention. Furthermore, none of these aforementioned studies have provided evidence regarding cost-effectiveness. Hence, to fill in this crucial knowledge gap to assist decision makers and clinicians, we constructed a Markov Model to compare the cost-effectiveness of OGD-based focused surveillance and mass screening. Our main objectives were to: (1) inform the choice of optimal strategy for secondary prevention of GC within the context of the Singapore healthcare system; and (2) provide suggestions for actual implementation of a GC screening or surveillance program in a country at intermediate GC risk. Besides providing information about cost-effectiveness of various programs for the decision makers in Singapore, our model could be adapted for use in other locales. While the cost and outcome values are expected to be different in different jurisdictions, our model can provide a valid platform for performing cost-effectiveness analysis of such programs by populating it with local data.

5.2 Research Frame of Cost-Effectiveness Analysis Endoscopic Surveillance

5.2.1 Target population

The target population was defined as Chinese aged 50-69 year old. According to Singapore Cancer Registry (Singapore Cancer Registry Committee 2012), there is a sharp increase in GC risk after the age of 50 years and the defined population carries most of GC burden (90%).

Although people aged 70 years or older have even higher risk of GC, they are not recommended for preventive programs for two reasons: (1) the possibility of extending their life expectancy is slim given their old age, and the extra OGD examinations and ensuing clinical management are proven unnecessary and ineffective (Dan, So and Yeoh 2006); and (2) compliance in this age cohort is always low, as a consequence, cost effectiveness is not satisfactory (Cho et al. 2013). Furthermore, as data suggests (Ministry of Health 2004), a 70-year person tends to suffer from multiple comorbidities with most prevalent diseases being diabetes and heart disease. These competing diseases make GC screening less of a health priority, especially when the subject does not present with gastric symptoms (Kye, Han and Park 2010).

5.2.2 Endoscopy/Biopsy protocol

OGD/biopsy protocol is standardized in consideration of test characteristics of sensitivity and specificity, and social factors of accessibility and availability of endoscopy in Singapore healthcare system. The OGD/biopsy protocol consists of two parts: 1) ordinary OGD examination to identify stomach lesions based on morphologic alteration of stomach mucosa, and 2) detailed biopsy to provide histological results.

Six sites defined as below were selected for sampling (Figure 5-1).

1) A1- lesser curvature of the antrum, within 2-3cm of the pylorus;
2) A2- greater curvature of the antrum, within 2-3cm of the pylorus;
3) IA- incisura angularis;
4) B1- lesser curvature of the corpus, 4cm proximal to the angulus;
5) B2- middle portion of the greater curvature of the corpus, 8cm from the cardia;
6) Cardia (C) - within 1 cm below the OGJ (defined as the point where gastric folds disappear).

Stomach mucosa will be biopsied each from A1, A2, IA, B1, B2 and C, and fixed for histology. The fresh biopsy from A1 will be used for Helicobacter pylori genotyping. This standardized procedure is used in both screening and surveillance in this project.

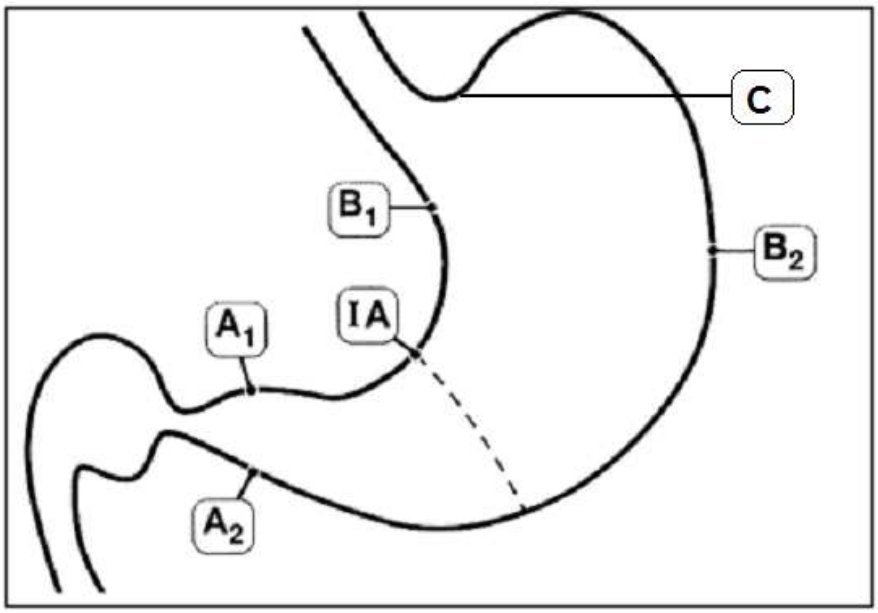


Figure 5-1. Biopsy sites during endoscopy examination in screening and surveillance

5.2.3 Strategies in consideration

A decision analytic model was previously used to explore the cost-effectiveness of secondary prevention of GC in the same target population. The authors recommended that 2-yearly OGD screening is cost-effective for GC prevention in Chinese males age 50-70 year old (Dan, So and Yeoh 2006). Since 2-yearly OGD screening is already an option in Singapore, we felt compelled to make a

head-to-head comparison between surveillance and screening, following good practice of modeling study (Weinstein et al. 2003).

5.2.3.1 Endoscopic screening

To implement the 2-year OGD screening, the target population would be divided into two halves. In any given year, only one half of the population undergoes follow-up OGD. In this way, the two halves undergo OGD in tandem so that the entire target population undergoes an OGD examination once every two years. Our model assumed that the OGD follow-up will continue until a subject dies or is diagnosed with GC.

5.2.3.2 Endoscopic surveillance

For OGD surveillance, the defined target population would be screened at baseline with a standardized OGD procedure (Figure 5-2). *H. pylori* infection, if detected, would be eradicated using the standard triple-therapy regimen (Talley, Fock and Moayyedi 2008). We based the recommendation of OGD follow-up on histological examination of stomach mucosa. Those presenting with precancerous lesions (Bustamante et al. 2002; El-Zimaity et al. 2001; Graham and Asaka 2010; Kapadia 2003; Whiting et al. 2002) will be categorized as high risk subjects and would be subjected to annual OGD follow-up. Those without precancerous lesions would be categorized as low risk, and would not require further ODG follow-up. The number of subjects undertaking OGD surveillance is determined by the prevalence of premalignant gastric lesions. As in the screening strategy, OGD follow-up will continue until a subject dies or is diagnosed with GC.

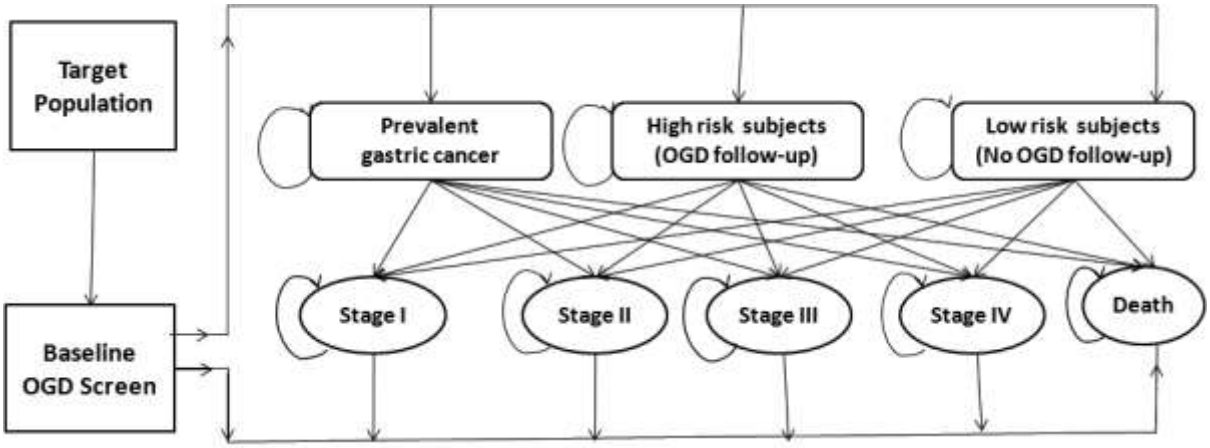


Figure 5-2. Overview of the surveillance strategy

5.2.4 Determination of societal willingness-to-pay

Following the guidelines of World Health Organization (Commission on Macroeconomics and Health 2001), the Singapore GDP of $46,200 per capita for year 2011 was used as the willingness-to-pay (WTP) threshold. The GDP is country-specific so this WTP of $46,200 /QALY serves as a benchmark unique to Singapore in judging the cost-effectiveness of the evaluated strategy. A strategy associated with an ICER less than $46,200/QALY is considered cost-effective in our project.

5.3 Markov Model Development

The decision-analytic model most commonly used for disease simulation is the Markov model (Barbosa et al. 2010). Markov model is a state transition model which is able to simulate the dynamics of disease and associated clinical intervention over a long period of time in a specified population. We adopted a healthcare system perspective instead of a societal perspective, as one of the major purposes of this project is to inform the implementation of a surveillance program within the Singapore healthcare system.

In this chapter, we illustrated the process of model construction step by step using TreeAge software version Pro 2009 (TreeAge Software, Inc., Williamstown M.A., USA). We provided detailed explanations about the theories and thoughts regarding model structure, equations, parameter values, assumptions and some TreeAge techniques. By presenting the model this way, we aimed to give readers a clear picture about Markov model construction and allow them to evaluate our model at high level of mathematical and clinical detail. As the model is designed to have multi-applications, we hope that, with appropriate modification of our model, readers can develop their own models to address their specific research problems.

5.3.1 Thought experiment before model development

To the best of our knowledge of the natural history of GC and related clinical practice, we have presented an overview of the clinical pathways of the target population at GC risk using a simple schematic diagram (Figure 5-3).

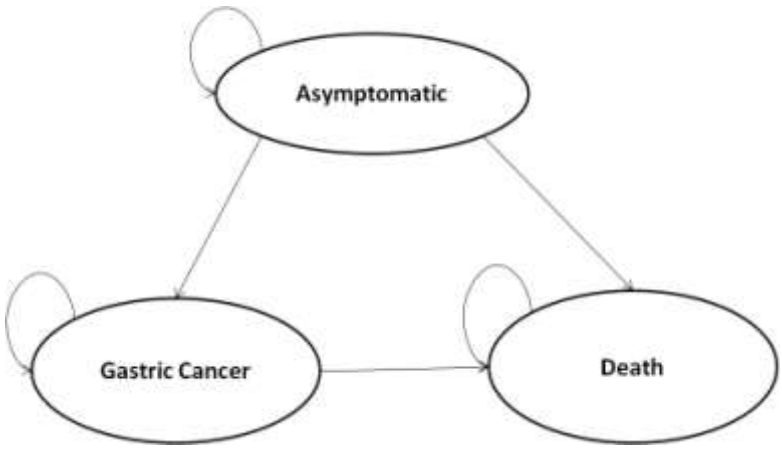


Figure 5-3. Overview of clinical pathway of target population developing gastric cancer

Arrowed lines represent transitions from one state to a different state. If a subject remains in original health state, an arrowed curve was used.

Three mutually exclusive health states were defined (Figure 5-3). A subject in an asymptomatic state means that the person is free of GC, and therefore considered healthy in general; a Gastric cancer state

means a subject has been diagnosed and is currently living with GC; and a Death state indicates the death event to either a healthy person or GC patient. In any given year (a Markov cycle in our model), a subject of the target population stays in only one of three health states. Transitions among health states were driven by the clinical events of death and diagnosis of GC. As shown in Figure 5-3, once a subject is diagnosed with GC, biologically he is not able to regress to a state of being GC-free, reflecting that biologically there is no cure for a cancerous disease. A person who is already dead cannot return to a state of being alive, asymptomatic or Gastric Cancer. The Death state is called the absorbing state in the Markov model.

As stated in Chapter II, the cancer staging is important in guiding clinical management and public health programs. To evaluate the down-stage effect of preventive strategies, it is necessary to present the clinical stages of GC in our model, which would be represented by additional Markov states. Therefore, the GC state in Figure 5-3 was divided into four states corresponding to the clinical staging system of GC (Clinical Stage 1, Clinical Stage 2, Clinical Stage 3 and Clinical Stage 4) (Figure 5-4).

In Figure 5-4, we highlighted the problem associated with the current practice of no OGD prevention. At present, Singapore has not yet installed public health programs for GC prevention. The majority of GC patients are diagnosed with advanced cancer (Stage 3 & Stage 4) (Koong et al. 1996) when treatment is not so effective in prolonging survival or improving quality of life.

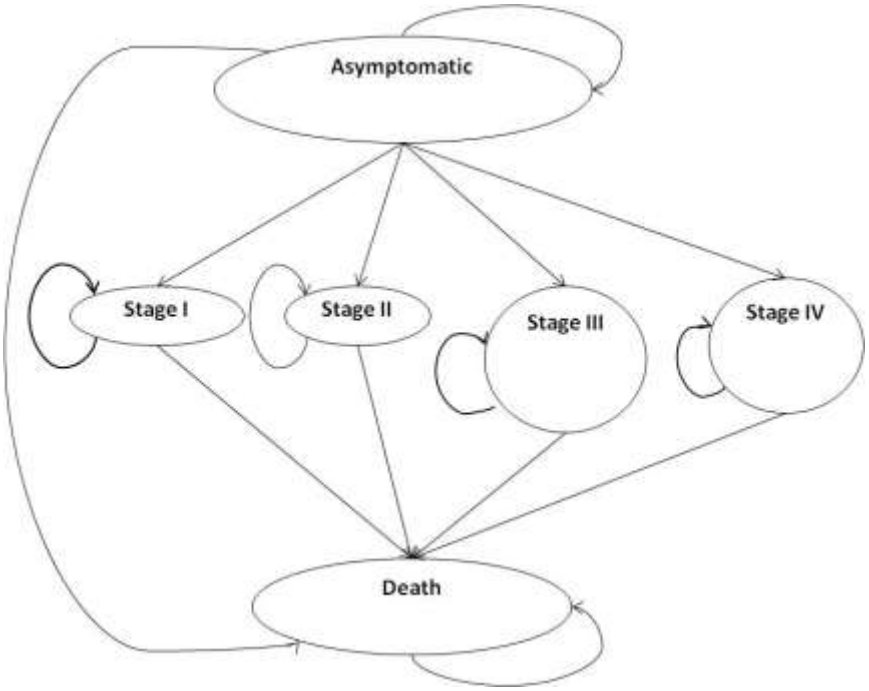


Figure 5-4. Overview of clinical pathway of present situation without gastric cancer prevention

1) Arrowed lines represent transitions from one state to another. If a subject remains in the original health state, an arrowed curve was applied.2) The area of the cycle represents the proportion of each clinical Stage in diagnosed GC cases

However, as shown in Figure 2-1, GC development is a years or even decades-long process (Liu et al. 2006). Accordingly, there is a long preclinical phase during which clinical interventions like screening or surveillance are capable of detecting gastric premalignancies and potentially making earlier diagnoses of GC. With scheduled OGD follow-up of patients with atrophic gastritis, intestinal metaplasia and dysplasia, it could be expected that a greater proportion of GC cases are diagnosed with early stage diseases (Nakashima et al. 2010), in contrast to the usual care where the majority of GC patients have advanced disease (Wai et al. 2002). This shift of stage distribution of GC patients is called the down-stage effect. Figure 5-4 and Figure 5-5 illustrate how secondary prevention causes down-stage.

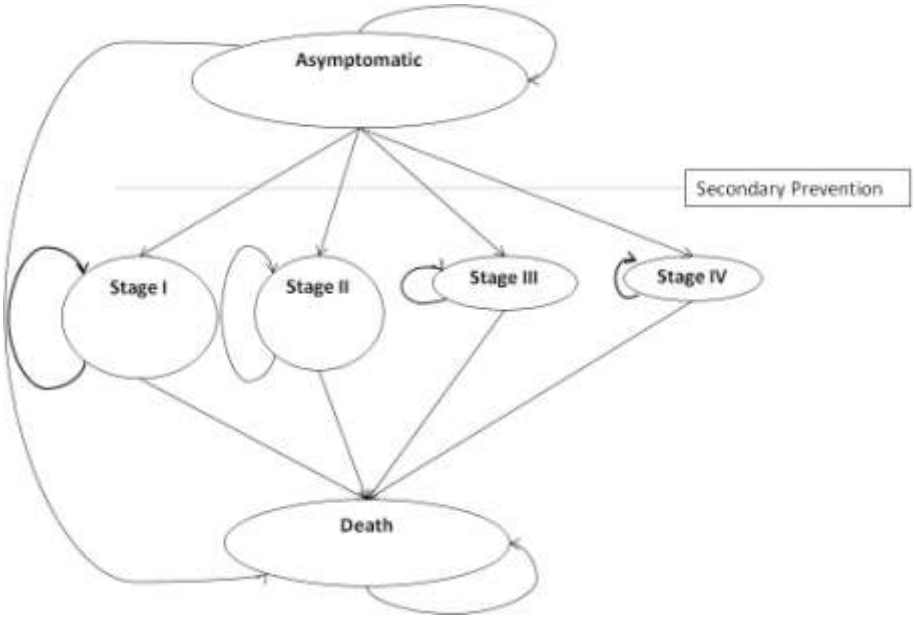


Figure 5-5. Expected effect of stage-shift by gastric cancer prevention programs

1) Arrowed lines represent transitions from one state to a different state. If a subject remains in original health state, an arrowed curve was applied.2) The area of the cycle represents the proportion of each clinical Stage 1n all diagnosed GC cases

5.3.2 Building Markov model with TreeAge software

We used the commercial software TreeAge to build the Markov model. TreeAge was chosen because the software is user-friendly, visually based and less prone to mistakes than program-based software like Microsoft Excel (Menn and Holle 2009). TreeAge presents the Markov model in a graphical form known as a cycle tree. Figure 5-6 shows the basic TreeAge structure comparing the Markov models for screening, surveillance and no OGD intervention.

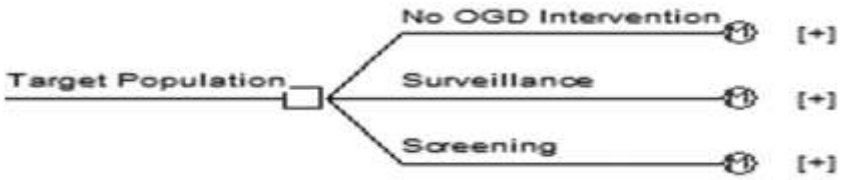


Figure 5-6. Basic TreeAge tree comparing screening, surveillance and no OGD intervention

The completed Markov trees are presented in the figures that follow.

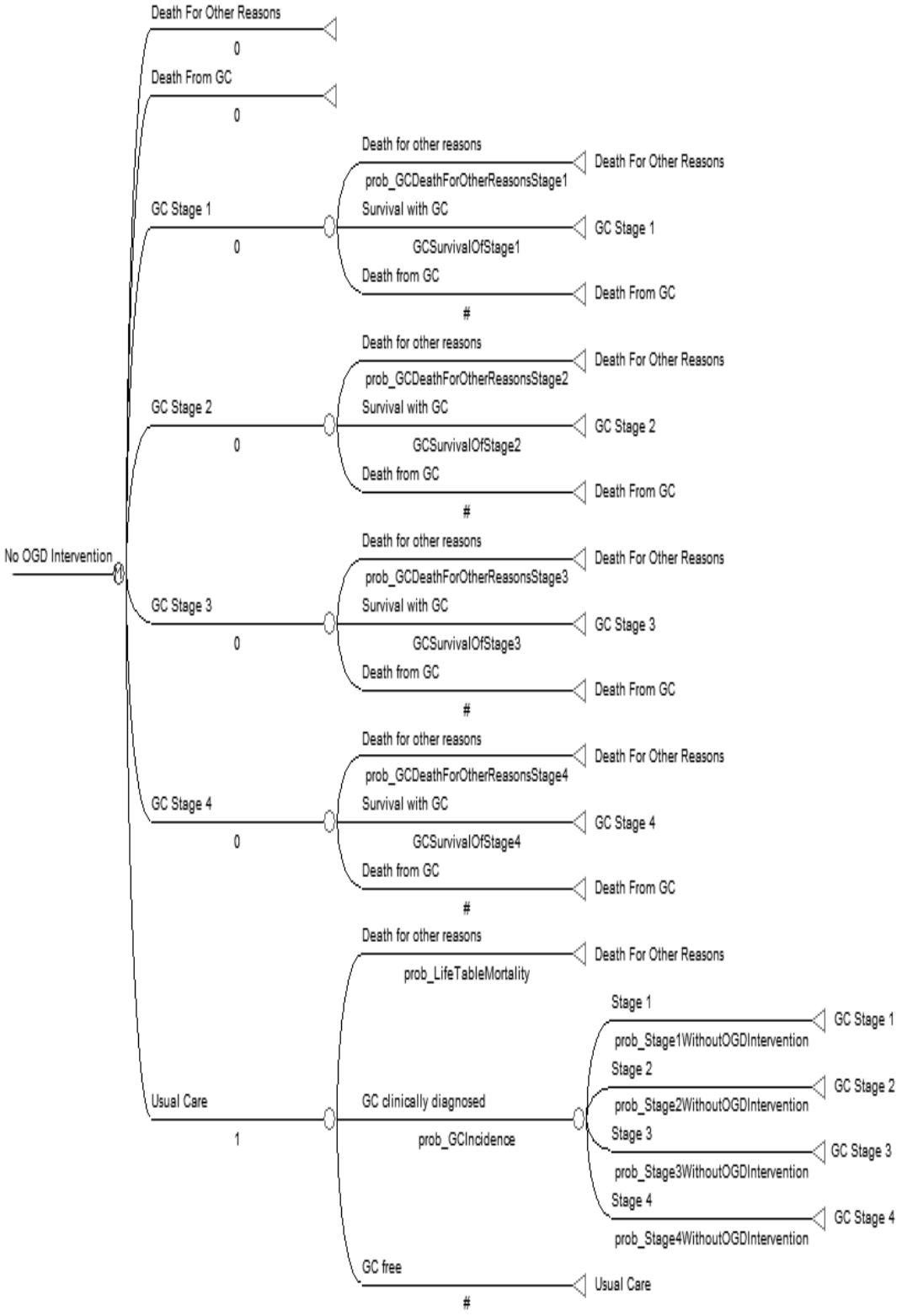


Figure 5-7. Markov Model for the no OGD intervention strategy

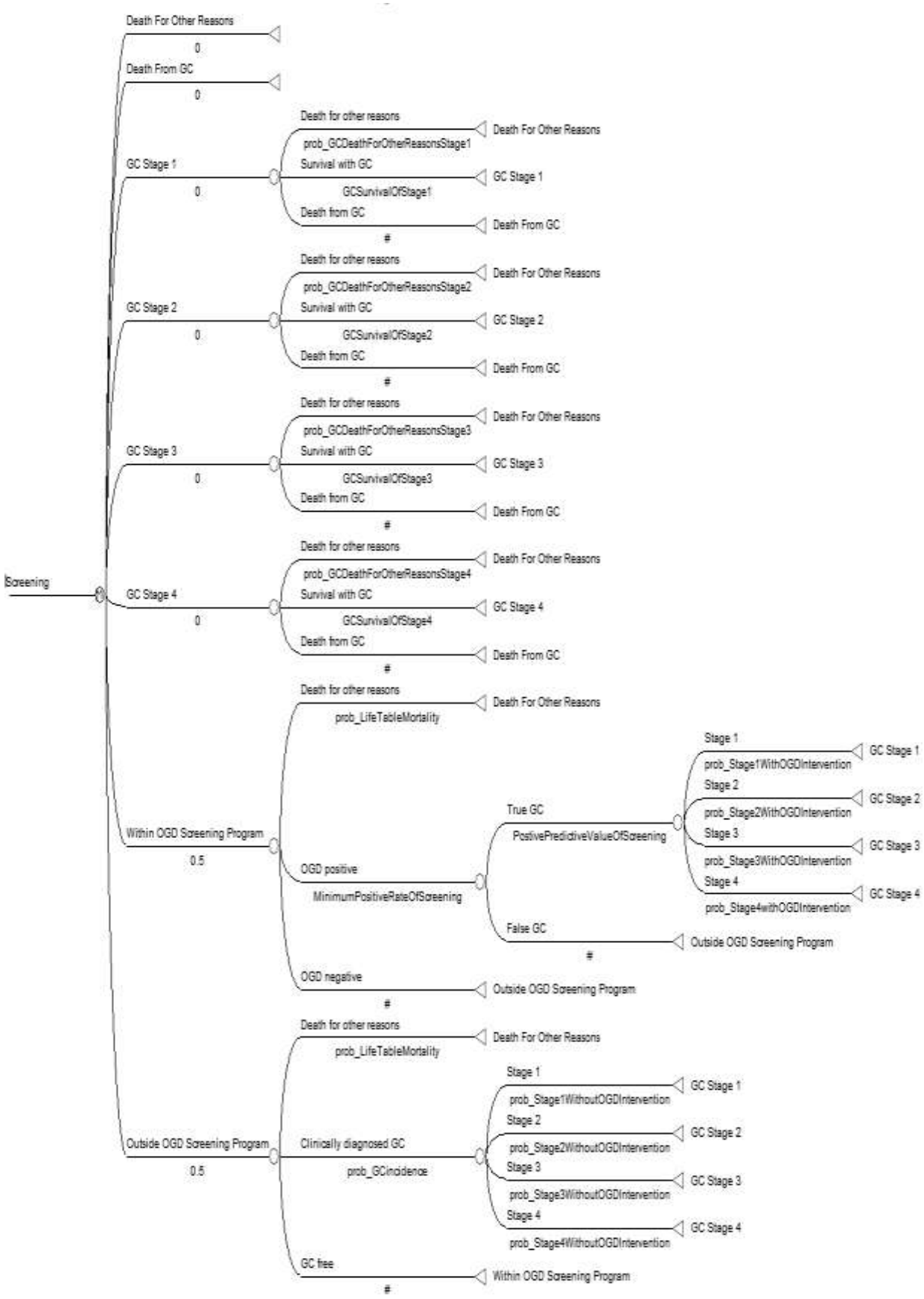


Figure 5-8. Markov Model for the screening strategy

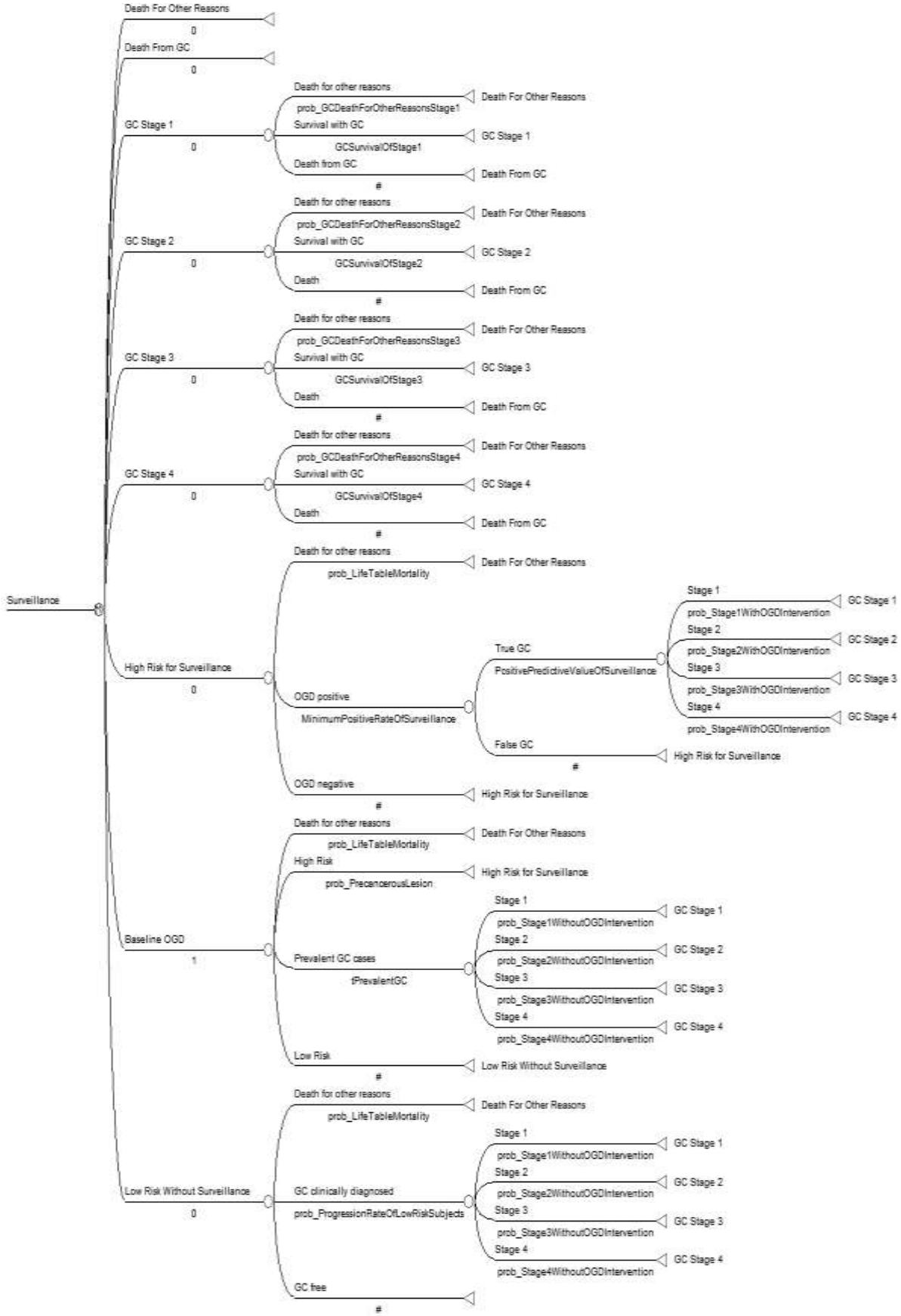


Figure 5-9. Markov Model for the surveillance strategy

5.4 Expansion and Population of the Markov Tree

Developing a simple diagram (Figure 5-4 and Figure 5-5) into a complex TreeAge Markov tree (Figure 5-7, Figure 5-8 and Figure 5-9) populated with a large amount of data constitutes the primary part of the modeling process. This process normally consisted of three parts: (1) defining Markov states which represent the major clinical events in the course of disease prognosis; (2) designing a Markov model structure to simulate clinical pathways composed of Markov states. The complexity of the structure is jointly determined by the availability of data and the extent to which the modeler wishes to reflect clinical reality; (3) populating the Markov model with the best-available data about diagnosis, treatment, disease history, epidemiology, cost and utility. The target population was modeled year by year until 99% of the cohort died, which is the termination condition for a TreeAge programmed Markov model.

Defining Markov states: Based on the thought experiments, we defined seven Markov states for no OGD intervention strategy, namely, asymptomatic (branch *"usual care"*, Figure 5-7), GC stage 1, GC stage 2, GC stage 3 and GC stage 4, death from GC and death for other reasons. The asymptomatic state was divided into two categories for the screening strategy representing alternate OGD examination of the target population (branch *"without OGD screening program"* and branch *"outside OGD screening program"* Figure 5-8). For the surveillance strategy, the asymptomatic state was divided into three categories corresponding to three populations with different GC risk (branches *" high risk for surveillance"*, *"low risk without surveillance"* and *"baseline OGD"*, Figure 5-9). The Markov states representing death event and GC stages are the same for all the three strategies.

Designing Model structure: Based on the diagrams of Figure 5-4 and Figure 5-5, TreeAge model structure was designed to depict the clinical pathway which the target population will go through each of the three strategies. In any given model, the simulation starts with the asymptomatic state, i.e. the target population is at risk of GC but clinically is free of the malignancy. As the model progresses,

some individuals of the cohort develop GC. These GC patients are diagnosed with different clinical stages and represented by the Markov states for clinical stages in the models. GC patients subsequently receive standardized stage-specific treatment therefore achieve stage-specific survival. GC patients and healthy subjects all are exposed to background mortality. Finally, the total cohort reaches its life expectancy and the model terminates the simulation. For the screening and surveillance process, the models incorporated the practice of OGD follow-up.

Data synthesis: As we retrieved data from various study designs, it would be inappropriate to use them in the model without carefully evaluating their quality in terms of internal validity, reliability and generalizability to our situation. Published data were the primary sources for parameters inputted in our model. In the event that required data were not available in publications, expert opinions (Dr. Dan Yong Yock, a consultant gastroenterologist in NUH) were sought as the best estimates (Weinstein et al. 2003). Data which were obviously "outliers" would not be used. Any reasonable data range would be identified for the subsequent sensitivity analysis. TreeAge techniques were tried and tested to ensure that the data were accurately represented when the model runs.

The modeling started with no OGD intervention because it is technically simple. Upon completion of that Markov tree, the model structure was modified to incorporate the additional data associated with the screening and surveillance strategies to be evaluated. The skeletons of the Markov subtrees were consistent thus improving the comparability between the three strategies. The following sections illustrate how we handled the important issues in constructing Markov models. We presented the contents by showing how the information was treated differently among the three strategies.

5.4.1 Gastric Cancer Development in the Target Population

5.4.1.1 Gastric Cancer Development with no OGD Intervention

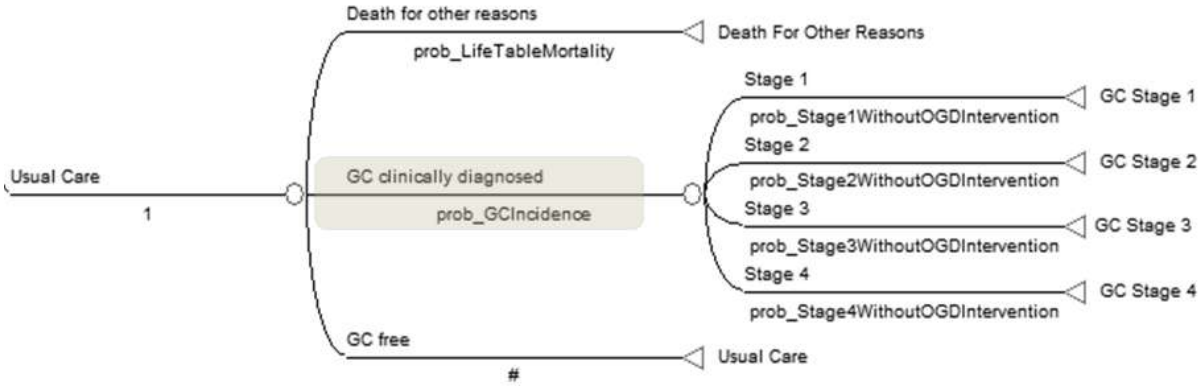


Figure 5-10. Gastric cancer development in the general population with no OGD intervention

As in Figure 5-10, GC occurrence in the target population was denoted by the branch *GC clinically diagnosed* (highlighted) indicating that GC patients in Singapore are diagnosed in a general clinical setting. The probability of developing GC in a healthy population was estimated by incidence data from the Singapore Cancer Registry a population-based survey conducted every 5-years in Singapore (Singapore Cancer Registry Committee 2012).

We did not use point estimation of GC incidence for the target population (27.6/100,000), as it provides no information about the incidence variation by age and gender (Table 5-2). For the purposes of data precision, information from Table 5-2 was applied in the model.

The original data of the Registry was organized in 5-year age cohorts, which assumes that each 5-year cohort is homogeneous in terms of GC risk. For example, the incidence of GC in the 50-54 age cohort is 12/100,000, implying that the GC risk is the same for a person of 50 years as that for a person of 54 years old. However, given the positive association between age and GC risk (Guggenheim and Shah 2013), a 54-year person has a higher GC incidence than a person aged 50 years. Using the overall incidence of 5-year cohorts GC risk for younger age groups within that cohort were overestimated,

but underestimated for older age groups. Justifying its use in the model, we were forced to assume that the overestimation will be offset by the underestimation, which may not always hold true as the population size shrinks for older age cohorts. To fit the yearly Markov cycle, the information in Table 5-2 was reorganized as yearly data as in Table 5-3

Population incidence as reported by the Registry was the best available data to represent GC risk in Singapore. This practical limitation due to data availability is unavoidable for any modeling study. However, the Registry data can reflect the age trend of GC risk to a reasonable extent. These trends are more precise than a point estimate for the entire target population.

Table 5-2. Gastric cancer incidence reported by the Singapore Cancer Registry (1/100,000)

Age	Overall	Male	Female
50 - 54	**12**	**13**	**11**
55 - 59	**19**	**26**	**13**
60 - 64	**36**	**50**	**22**
65 - 69	**69**	**93**	**48**
70 - 74	105	157	61
75 - 79	193	284	123
80 & over	194	295	133

The age groups in bold are our target population.

TreeAge technical specification:

Table 5-3 is age and gender-indexed. When the target population survives one Markov cycle, TreeAge will choose the incidence corresponding to the cohort's age and gender until the model terminates. If a subject is modeled above the age of 80 years, the risk of GC remains at the incidence of an 80-year age cohort thereafter.

Table 5-3. Gastric cancer incidence by age and gender in the Markov model (1/100,000)

Age	Overall	Male	Female	Age	Overall	Male	Female
50	12	13	11	70	105	157	61
51	12	13	11	71	105	157	61
52	12	13	11	72	105	157	61
53	12	13	11	73	105	157	61
54	12	13	11	74	105	157	61
55	19	26	13	75	193	284	123
56	19	26	13	76	193	284	123
57	19	26	13	77	193	284	123
58	19	26	13	78	193	284	123
59	19	26	13	79	193	284	123
60	36	50	22	80	194	295	133
61	36	50	22				
62	36	50	22				
63	36	50	22				
64	36	50	22				
65	69	93	48				
66	69	93	48				
67	69	93	48				
68	69	93	48				
69	69	93	48				

(Singapore Cancer Registry Committee 2010)

5.4.1.2 Gastric Cancer Development under the Screening Strategy

Screening, as a secondary prevention strategy aiming for early detection, is not supposed to change the GC risk, i.e. GC incidence (Lee et al. 2006; Tsubono et al. 2000). The screening strategy evaluated in our study involves a 2-year cycle consisting of one year with OGD examination and the other year without. Therefore, although the GC incidences are the same for screening-years and non-screening-years, the data have to be treated differently (Figure 5-8).

As shown in Figure 5-11, during non-screening-years (branch *"outside OGD screening program*"), the GC development in the target population was represented by the incidence data of the Registry as used in the no OGD intervention (branch "*clinically diagnosed GC*").

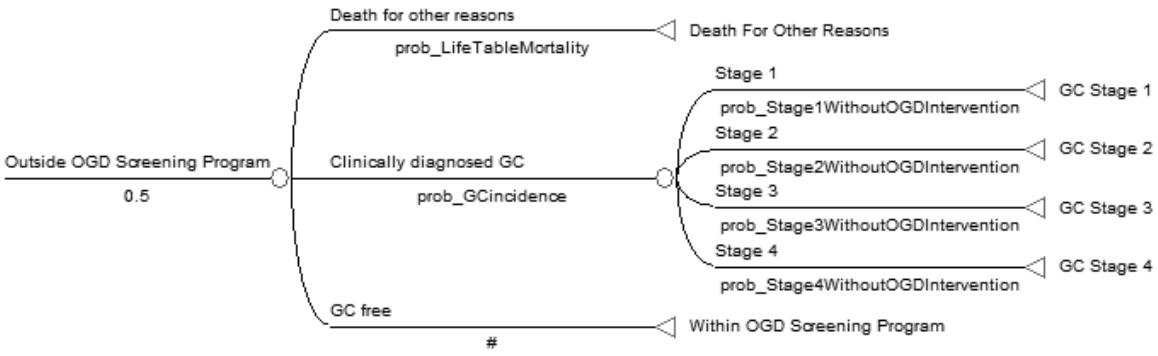


Figure 5-11. Gastric cancer detected during years without follow-up OGD

However, during the screening-years of the screening strategy (Figure 5-12, branch *within OGD screening program*), the model should account for characteristics of the screening test, which refer to the sensitivity and specificity of OGD examination in particular.

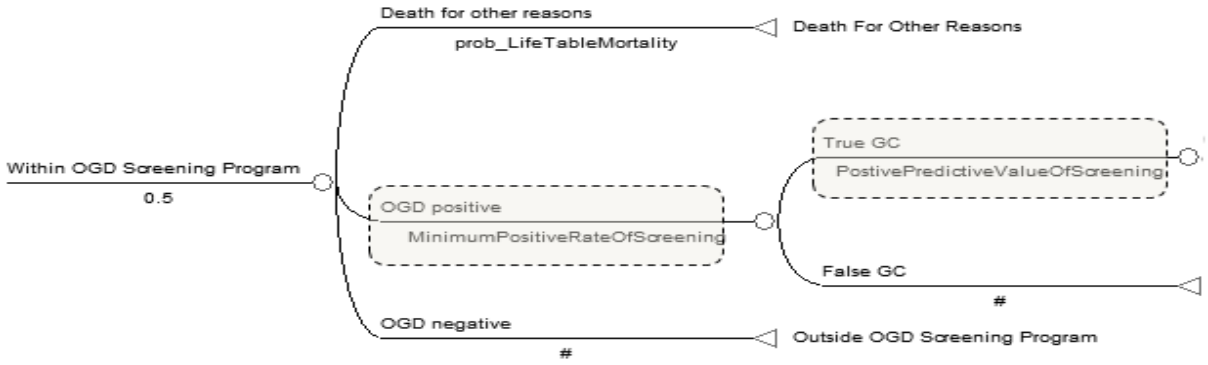


Figure 5-12. Gastric Cancer detected by screening OGD

To correctly simulate the influence on GC incidence by the screening strategy using OGD with given sensitivity and specificity as a screening tool, we had to examine the mechanisms of secondary prevention. In theory, OGD screening is unable to change the GC incidence. In reality, a screening program would definitely detect at least the same number of GC cases as no OGD intervention, if not more cases as a result of false positive and over-diagnosis (Tomizawa et al. 2013). Therefore, in building the structure of Figure 5-12, we assumed that all false positive cases (branch "*False GC*") were identified and excluded by confirming tests and that there were no over-diagnosed cases. This practice is considered acceptable (Knudsen,McMahon and Gazelle 2007).

The branch *True GC* denotes the GC patients detected by the screening program. Its associated probability is *Positive Predictive Value (PPV)* conditional on a positive screening OGD whose likelihood is denoted by *Minimum Positive Rate Of Screening* given the GC risk in the target population. Mathematically, the product of the *Minimum Positive Rate Of Screening* and *Positive Predictive Value (PPV)* results in the GC incidence projected by the structure of Figure 5-12. In TreeAge, a function called *Bayesian Revision* was enabled to carry out these computations using the input parameters of the sensitivity and specificity of OGD and population GC incidence. Consequently, the screening strategy projected a GC incidence similar to those reported by the Singapore Cancer Registry.

5.4.1.3 Gastric Cancer Development under the Surveillance Strategy

For the surveillance strategy (Figure 5-2), risk of developing GC was assessed in three subgroups, i.e., in the general population at baseline (Figure 5-13, branch *Prevalent GC Cases*), in high risk cohort (Figure 5-15, branch *OGD positive*) and in low risk cohort (Figure 5-14, branch *GC clinically diagnosed*). Since GC risk is different in these three groups (general population, high risk and low risk cohorts), the GC incidence data were adjusted to reflect this variation of GC risk as follows.

5.4.1.3.1 Gastric cancer development in the general population at baseline

As shown in Figure 5-2, a baseline OGD was administered to the target population to identify the high risk subjects with precancerous lesions. Actually, GC patients would be also detected at the same time (Figure 5-13, branch *Prevalent GC cases*). The GC patients diagnosed this way are referred to as prevalent cases indicating that they are existing cases not yet diagnosed and thus there is no benefit of early detection by screening. These cases (Figure 5-13, variable *tPrevalentGC*) were represented by the original incidence data from the Registry as used in the Markov tree for no OGD intervention.

One may argue that GC prevalence, rather than GC incidence, should be used at this point. However, prevalence by definition not only includes these prevalent cases, but also GC patients who were previously diagnosed and therefore ineligible for the screening. Using GC prevalence in our model would overestimate the GC case-load for the strategy.

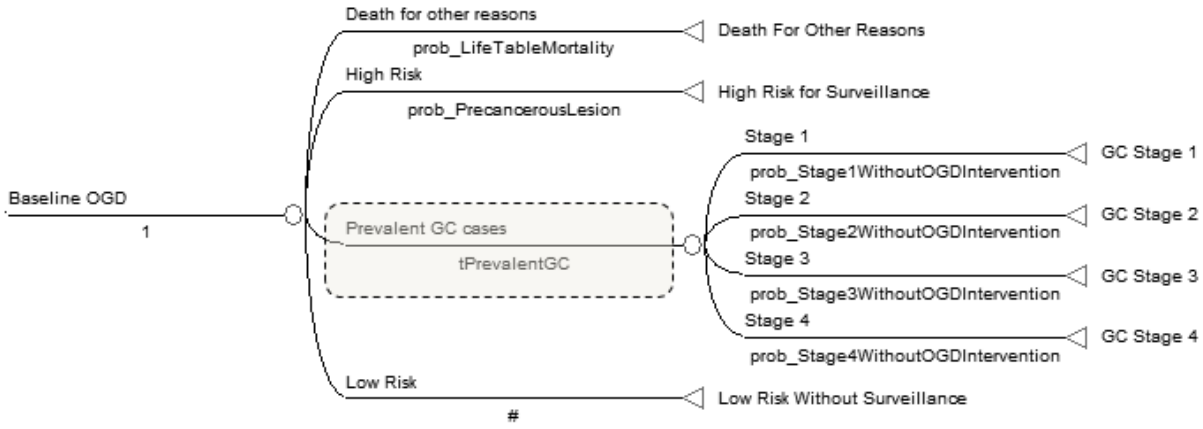


Figure 5-13. Gastric cancer development at baseline of the general population

5.4.1.3.2 Gastric cancer development for high and low risk cohorts

The key characteristic of surveillance in contrast with screening is to differentiate the target population by risk of developing GC. In the case of our surveillance strategy, the target population would be dichotomized into high and low risk cohorts at a baseline OGD examination of stomach mucosa. The high risk cohort comprises persons with precancerous gastric lesions. However, the precancerous lesions evaluated in our model were broadly defined. This point is different from previous studies (Dinis-Ribeiro et al. 2007; Hassan et al. 2010; Yeh,Ho and Hur 2010; Yeh et al. 2010) which defined the specific precancerous lesion in their modeling. In those studies, incidence rates indicating GC progression have to be estimated individually from external resources.

Using a broad definition for precancerous lesions, our model emphasized the excessive GC risk measured as odds ratios (OR) for GC attributable to certain gastric lesions. Then by simulating the effect of distinctive ORs on the model outcomes, our model is able to examine a wide spectrum of gastric lesions. To estimate GC incidences for high and low risk cohorts, we adopted an

epidemiologic concept called Attributable Risk, with the GC incidence of low risk subjects given by the following equation.

Incidence/ {[(OR-1)*Prevalence-of-Precancerous-Lesion]+1}

Equation 1. Progression rate of gastric cancer in the low risk cohort

The GC incidence of high risk subjects is given by the following equation.

Incidence*OR/ {[(OR-1)*Prevalence-of-Precancerous-Lesion]+1}

Equation 2. Progression rate of gastric cancer of the high risk cohort

Actually, these two equations are adjusted forms of attributable risk to calculate the incidences of cohorts with specific ORs in a single population.

Similarly as for the Markov models of screening and no OGD intervention, Equation 1 and Equation 2 use age and gender specific incidences in Table 5-3. Gastric cancer incidence by age and gender in the Markov model (1/100,000) in the TreeAge model is shown in Figure 5-14 and Figure 5-15.

The second parameter in the equation is the OR, which quantifies the GC risk attributable to precancerous lesions in the target population. With OR incorporated into the two equations, the GC risk estimated for the two risk cohorts which are clinically categorized by surveillance OGD, will be linked epidemiologically. As a consequence, the overall GC risk of the target population remains constant when our model simulates surveillance scenarios involving different precancerous gastric lesions. If the progression rates were estimated separately from different studies, this would risk the mistake that the overall GC risk would change in different scenarios.

The third and last parameter in the equations is the prevalence of the precancerous lesion. This parameter has to come from a Singapore-based population study because our study is stringently

Singapore specific. Even though there may be no well-designed survey to give a reliable estimate, the Markov model can examine the influence exerted by the variation of the prevalence of precancerous lesions using deterministic and/or probabilistic sensitivity analysis. This approach may be useful for decision-making.

Using the incidences from the Singapore Cancer Registry, ORs and prevalence of precancerous lesions in the two equations has helped to improve the comparability among Markov models in our project and avoid the problem of data transferability. As a result, the model is more Singapore-specific, clinically relevant and less dependent on the quality of external data. This is considered good practice by experts (Drummond 2005).

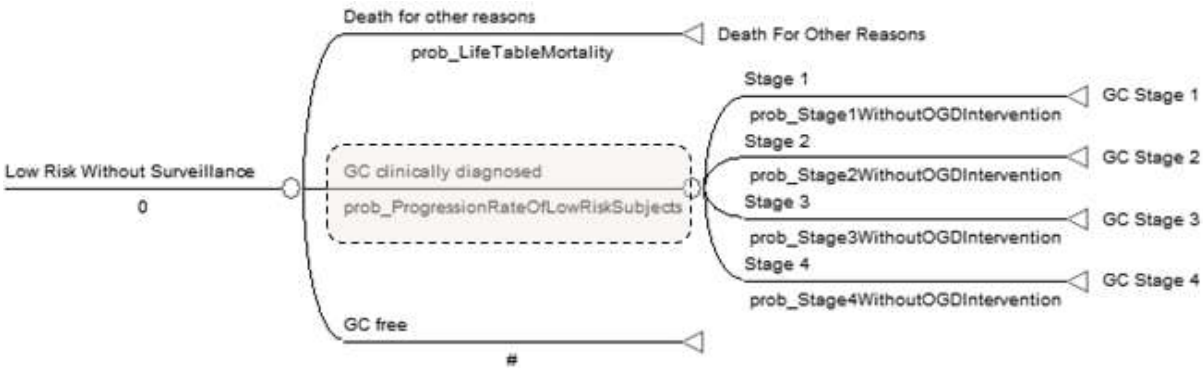


Figure 5-14. Gastric cancer development in the low risk cohort

In the Markov structure for the low risk cohort, Equation 1 was used to represent the progression rate from asymptomatic to GC (Figure 5-14, variable *prob_ProgressionRateOfLowRiskSubjects*). For the high risk cohort, Equation 2 was represented by the product of *MinimumPositiveRateOfSurveillance* and *PositivePredictiveValueOfSurveillance* in Figure 5-15.

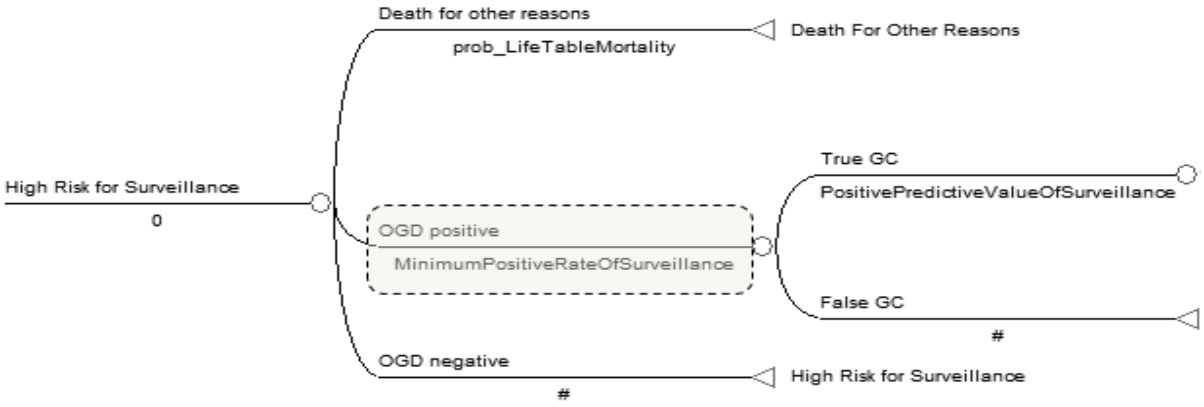


Figure 5-15. Gastric cancer development in the high risk cohort

5.4.2 Gastric cancer survival

When building the Markov models, we assumed that the survival experience after a diagnosis of GC would be the same irrespective of how the disease is diagnosed. For example, the annual probability of survival for a Stage 1 GC case is the same whether it is detected by a screening or surveillance OGD or diagnosed clinically under usual care of no OGD intervention.

After the diagnosis of GC, two distinctive clinical phases were defined as they had different clinical management strategies and accordingly different probabilities of survival. Phase 1 referred to the initial six months being diagnosed with cancer, during which a GC patient would receive aggressive diagnostic and therapeutic procedures. The probability of death in this phase was relatively higher (Environmental Protection Agency USA 2000; Munene et al. 2012). If the patient survived the acute treatment, he entered the Phase 2 when medical care was relatively less aggressive and the probability of death was stable.

5.4.2.1 Gastric cancer survival in Phase 1 (within six months after diagnosis)

The preliminary model has simulated two phases of GC survival. To model Phase 1, the TreeAge structure was initially designed as in Figure 5-16 (highlighted by bold boxes). Considering a real life scenario, GC patients can suffer an acute death from surgery, infection and complications of disease progression and chemotherapy, among others during Phase 1. The below structure requires the in-hospital mortality of GC patients.

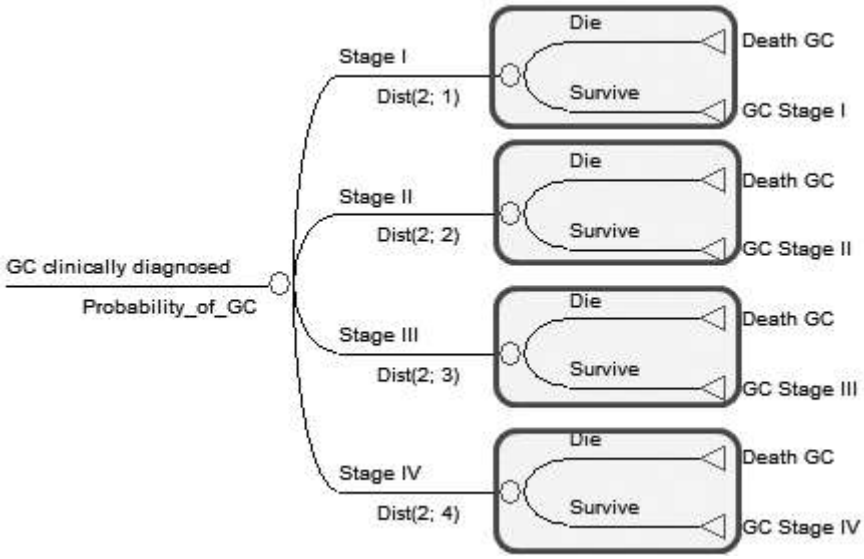


Figure 5-16. Gastric cancer diagnosis and treatment with simulation of in-hospital mortality

However, in-hospital mortality data is not available for Chinese patients with GC in Singapore. We have considered using the data reported for western populations (Wu et al. 2000). After consultation with one of the collaborators, Dr. Dan Yock Young, a senior consultant in gastroenterology, we decided that the non-Singaporean data were not transferrable to our setting, as this would compromise model validity. Thus we chose not to specifically model Phase 1 of patient survival. The TreeAge structure of Figure 5-16 was reduced to that shown in Figure 5-17.

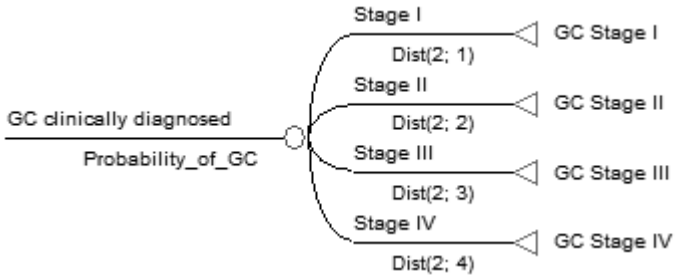


Figure 5-17. Gastric cancer diagnosis and treatment without simulation of in-hospital mortality

If in-hospital mortality data were available, they would be inputted into the Markov models for the three strategies. We believe that adding the same data into the models would only minimally affect the comparisons among the three strategies. In other words, even without detailed modeling on this phase, bias is unlikely. The limitation of our current models is that the survival rate in the first year could be slightly overestimated because of the exclusion of the in-hospital mortality data.

5.4.2.2 Gastric cancer survival in Phase 2 (after the first six months)

The second phase represents the clinical stage when the disease is generally stable under routine GC care, and thus the probability of survival is relatively low (Figure 5-18, branches *"Survival with GC"*). The annual probability of survival was derived from 5-year survival rates for each stage reported on the target population (Koong et al. 1996). The present model did not take into account of the effect on survival of age, gender or other variables. This practice is based on the assumption that the survival rate is generally homogenous in the patient cohort defined by the GC stage (Table 5-4).

Table 5-4. Annual probability of gastric cancer survival by clinical stage (%)

GC Stage	GC Survival
Stage 1	96.56
Stage 2	91.79
Stage 3	82.01
Stage 4	9.25

(Koong et al. 1996; Singapore Cancer Registry 2011)

As in Figure 5-18, the four GC clinical stages are modeled separately and populated with stage-specific survival data. The simulation of the concurrent death event (due to GC or other reasons) is illustrated in subsequent chapters.

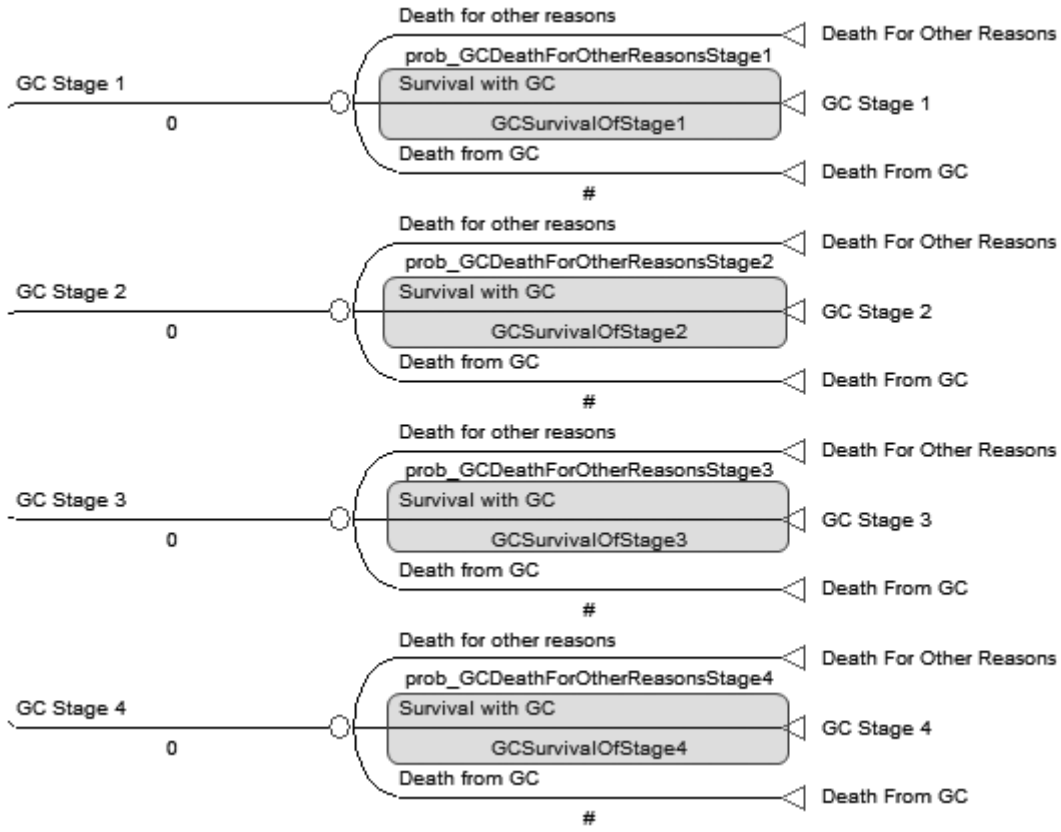


Figure 5-18. Stage specific gastric cancer survival

Stage-specific survival is the foundation for secondary prevention of GC. By separately modeling prognosis of GC patients of different stages, our model truthfully reflected the survival advantage of early stage GC cases that accounted for a bigger proportion of the patient cohort having been exposed to the screening or surveillance strategy. The favorable stage-shift due to the secondary preventive measures was translated into clinical outcome in our model.

5.4.3 Death

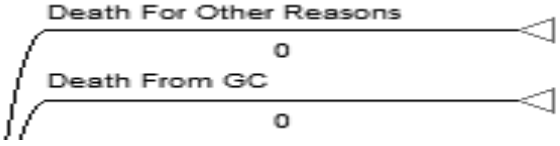


Figure 5-19. Death states in the Markov model

The mortality event in our model is classified into two categories by reason for death (branches *"Death from GC"* and "*Death for Other Reasons")*. This is to illustrate the effect of mortality reduction by early detection. Early GC patients have a better prognosis than those with advanced stage. Surveillance and screening strategies are designed to detect more early stage GC cases in comparison with the no OGD intervention and therefore achieve better survival of the target population. So we hypothesized that the GC-specific mortality represented by the Branch *"Death from GC"* would be smaller in the model outputs for the screening and surveillance strategy than that for the no OGD intervention.

"Death from GC" is straightforward in the model. *"Death for other reasons"* has to be considered in two different scenarios. The first scenario is presented in Figure 5-20 where *"Death for other reasons"* means the co-mortality due to other reasons for a healthy member. The second scenario is presented in Figure 5-21 where *"Death for other reasons"* means the competing mortality for a patient already diagnosed with GC. Mathematically, this mortality received different representation in the two scenarios.

5.4.3.1 Probability of death for other reasons for a healthy subject

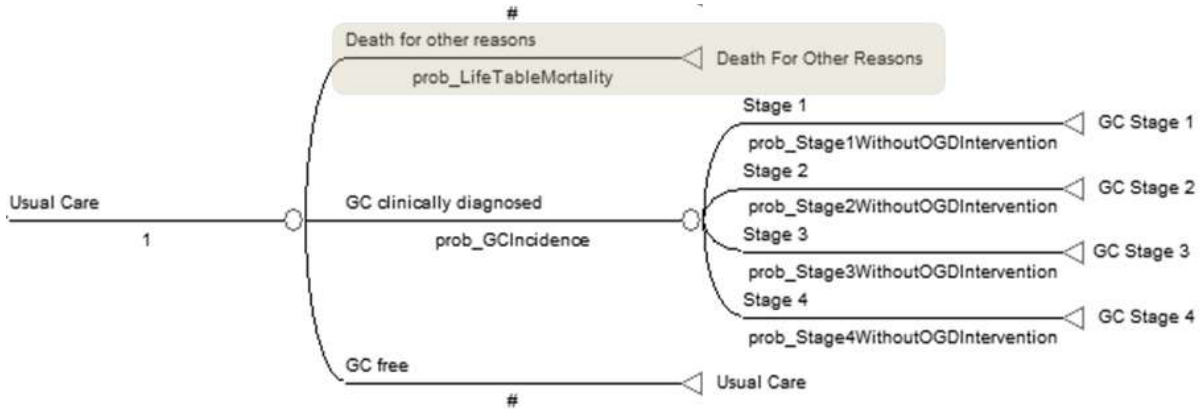


Figure 5-20. Co-mortality of the target population

The probability of death for other reasons for a healthy subject, or the co-mortality of the target population (Figure 5-20, branch *Death for other reasons*), was estimated by the age and gender-specific probability of dying reported in the Life Table of Singapore population 2011 (Department of Statistics Singapore 2012). The information from Table 5-5 was incorporated in the model to represent the co-mortality of the target population.

Table 5-5. Probability of dying at each age of the Singapore Chinese population

Age	Overall	Male	Female	Age	Overall	Male	Female
50	0.24%	0.31%	0.17%	76	3.18%	4.07%	2.47%
51	0.26%	0.34%	0.18%	77	3.52%	4.49%	2.78%
52	0.29%	0.37%	0.20%	78	3.91%	4.94%	3.13%
53	0.32%	0.41%	0.22%	79	4.31%	5.42%	3.51%
54	0.34%	0.45%	0.24%	80	4.72%	5.90%	3.90%
55	0.37%	0.49%	0.26%	81	5.14%	6.40%	4.30%
56	0.40%	0.53%	0.28%	82	5.62%	6.96%	4.74%
57	0.44%	0.57%	0.31%	83	6.19%	7.66%	5.27%
58	0.48%	0.63%	0.34%	84	6.86%	8.48%	5.89%
59	0.53%	0.69%	0.38%	85	7.56%	9.33%	6.55%
60	0.58%	0.74%	0.42%	86	8.33%	10.25%	7.27%
61	0.63%	0.81%	0.46%	87	9.16%	11.26%	8.06%
62	0.70%	0.90%	0.51%	88	10.07%	12.35%	8.93%
63	0.80%	1.02%	0.58%	89	11.07%	13.53%	9.87%
64	0.90%	1.17%	0.65%	90	12.15%	14.81%	10.91%
65	1.02%	1.32%	0.73%	91	13.32%	16.19%	12.03%
66	1.13%	1.48%	0.81%	92	14.59%	17.68%	13.26%
67	1.25%	1.64%	0.90%	93	15.96%	19.28%	14.59%
68	1.38%	1.81%	0.99%	94	17.45%	21.00%	16.03%
69	1.51%	1.98%	1.10%	95	19.05%	22.85%	17.59%
70	1.65%	2.15%	1.20%	96	20.77%	24.82%	19.26%
71	1.79%	2.34%	1.31%	97	22.62%	26.93%	21.07%
72	1.98%	2.58%	1.47%	98	24.60%	29.17%	23.00%
73	2.24%	2.91%	1.68%	**99**	**26.72%**	**31.55%**	**25.07%**
74	2.54%	3.28%	1.94%	**100**	**100%**	**100%**	**100%**
75	2.86%	3.67%	2.20%	101			

(Department of Statistics Singapore 2012)

The Life Table would slightly over-estimate this probability since GC contributed to the overall background mortality of the Singapore population (Singapore Cancer Registry Committee 2012).

However, this over-estimation is normally considered insignificant in comparative modeling studies (Weinstein et al. 2003).

As Life Table calculation aggregates the deaths after a person reaches 100 years, the death rate for an age cohort of 100 years increases to 100% from 26.7% for a 99-year age cohort (Table 5-5, highlighted in bold fonts). We extrapolated the oldest age to 101 years by assuming that a Chinese person is definitely dead in two years after age of 99 years. Then recalculating the probability of death for age cohorts of 100 and 101 year old produces the result of 1/2= 50%. Like incidence data, background morality is also integrated into the model in an age and gender-indexed table.

5.4.3.2 Probability of death for other reasons for a gastric cancer patient

As defined in 5.2.1, our target population is considered an aged cohort at baseline. Therefore, even though a subject is diagnosed with GC, there is still a high risk of dying of other causes such as cardiovascular disease (Guadagni et al. 1997), especially when GC is discovered later in life. As we model the lifetime experience of the target population, our Markov model has to take this issue into account (Figure 5-21, branch "*Death for other reasons"*).

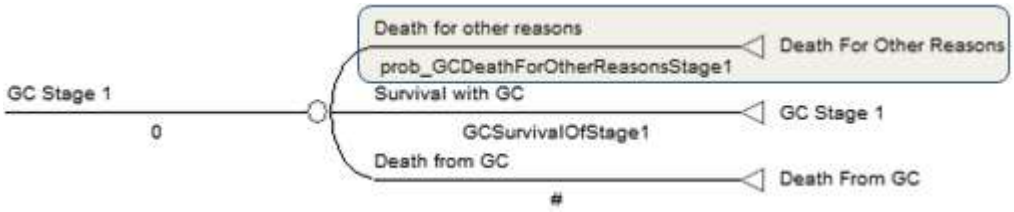


Figure 5-21. Death for other reasons of GC patients

The probability of a GC patient dying of other causes is not the same as the probability of someone in the general population, particularly in the first few years after diagnosis when the probability of GC death is relatively high. Therefore, we estimated the probability of death for other reasons in our

target population following the approach outlined in the 'Cost of Illness Handbook'. (U.S. Environmental Protection Agency 2010).

Table 5-6. Probability composition of gastric cancer patients surviving through a given year

p	**w**
q_1	**q_2**

Table 5-6 represents the cohort of GC patients who remain alive at the beginning of the year. The area of the entire box is the probability of having survived to the beginning of the given year post-diagnosis and assumes the probability of 100% at the initial Markov cycle. That is, all probabilities described below are conditional on having survived to the beginning of this given year post-diagnosis.

- **p:** The probability of a GC patient surviving through a given year post-diagnosis (GC survival rate for four clinical stages each)
- **q:** The probability of dying of causes other than GC in a matched cohort in the general population (Life Table).
- $\mathbf{q = q_1 + q_2}$, a mathematically hypothesized probability for calculation
- **q_2:** The proportion of the GC cohort who would die of other causes if they were not diagnosed with GC beforehand who instead die of GC.

$$\mathbf{q_2 = (q/(1-q) \times (1-p-q)}$$

For a GC patient, the probability of GC death during the given year (Markov cycle) is

$$\mathbf{P_{Cancer} = (1-p-q) + 0.5 \times q_2}$$

The probability of death for other causes during the given year (Markov cycle) is

$$\mathbf{P_{Other} = q - 0.5 \times q_2}$$

The annual probability of death for other reasons is presented Table 5-7. The cancer is still the main cause of death for a GC patient, despite the higher probability of death due to other reasons. As the

cancer becomes more advanced, the likelihood of dying of other reasons decreases which clearly is consistent with the clinical reality.

Table 5-7. Pattern of death in gastric cancer patients (%)

GC Stage	GC Survival	GC Death P_{Cancer}	Death for Other Reasons P_{Other}
Stage 1	96.56	2.09	1.35
Stage 2	91.79	6.89	1.32
Stage 3	82.01	16.74	1.25
Stage 4	9.25	90.00	0.75

5.4.4 Early detection by screening and surveillance

From an epidemiological perspective, early detection by screening or surveillance manifests itself as a favorable shift of stage distribution in GC patient population. That is, there should be more early stage cases in GC patients detected by the program than in the GC patient cohort diagnosed under routine clinical practice. In our model, we used two Dirichlet distributions to represent the stage-shift. The first Dirichlet distribution describes the stage composition under routine care. Stage 1: Stage 2: Stage 3: Stage 4: corresponds to 7%:17%:33%:43% respectively (Figure 5-22) (Kim et al. 2000; Kubota et al. 2000; Nakashima et al. 2010).

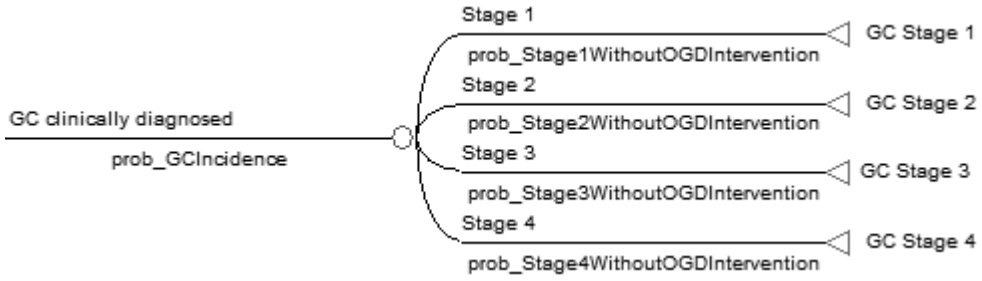


Figure 5-22. Stage distribution of gastric cancer patients diagnosed under usual care

The second Dirichlet distribution describes the stage composition of GC patients detected by preventive programs. The proportion of Stage 1, Stage 2, Stage 3 and Stage 4 patients are 85%, 4%, 8% and 3% respectively (Figure 5-23) (Koong et al. 1996; Wai et al. 2002). It is assumed that the down-

stage effect is independent of the frequency of follow-up OGD. So the second Dirichlet distribution was applied in the Markov tree for screening and surveillance.

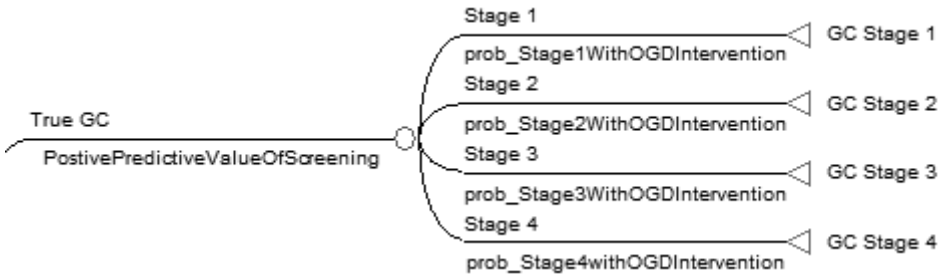


Figure 5-23. Stage distribution of gastric cancer patients detected by follow-up OGD

We did not define the range for each stage proportion for deterministic sensitivity analysis because clinically, the cancer staging of Stage 1, Stage 2, Stage 3 or Stage 4 are not independent events. The sum of four proportions has to be one, which is called Coherence of Probability. Defining individual ranges could violate this requirement when TreeAge program runs the models. Using two Dirichlet distributions has another advantage, that is, the variations of four proportions for each clinical stage can be explored later using probabilistic sensitivity analysis sampling.

5.4.5 Cost estimation

We estimated the incremental cost related to operation of an OGD surveillance or screening program, initial diagnosis and treatment, and post-treatment follow-up of GC patients. The main cost difference between preventive strategies and no OGD intervention is the expenditure on operating a screening or surveillance program. This expenditure is referred to as operational cost. Initial diagnosis and staging include gastrointestinal imaging, blood tests, endoscopy, biopsy, computed tomography scans and laparoscopy. GC treatment includes surgery, chemotherapy, radiation, and other general medical services. Post-treatment follow-up cost, in this case, includes blood tests, computed tomography scans and OGD examinations.

5.4.5.1 Operational cost and efficiency

The costs of operating a screening or surveillance program or operational cost were primarily comprised of two parts; the clinical cost of OGD and biopsy, and the non-clinical cost of supporting activities in the delivery of the OGD program, which include establishment of infrastructure and delivery system, manpower, case management, quality control, transportation and subjects' salary loss due to program participation (Table 5-8).

When estimating the clinical cost, we used the direct estimate from our precious study on cost efficiency of a OGD surveillance program for GC in Singapore (Zhou et al. 2013). For the non-clinical or program cost, we used its proportion of total operational cost to represent it in the model. That is, program costs and clinical costs are compared in a way given a certain operational cost, like a fixed budget for a program. The above mentioned proportion practically serves as an indicator of operating efficiency of an actual program (Centers for Disease Control and Prevention 2005; Subramanian et al. 2011).

Table 5-8. Operational cost for a screening or surveillance program

Components	Content	Cost $ Mean (Range)	Reference
Baseline OGD for surveillance strategy	OGD/biopsy/ *H. Pylori* eradication	350 (175-750)	
Follow-up OGD	OGD / biopsy	340 (170-680)	(Zhou et al. 2013)
Program cost (%)	Supporting activities	50% (20-80%)	(Subramanian et al. 2011) (Centers for Disease Control and Prevention 2005)

5.4.5.2 Treatment and follow-up cost

When estimating treatment cost, we followed the instructions recommended in 'The Cost of Illness Handbook' (Environmental Protection Agency USA 2000). The instructions are stated as follows:

1. Identify a cohort who has received the standard GC treatment. The hypothetical cohort consists of GC patients being treated in NUH, the not-for-profit tertiary medical institution

where physicians follow the international algorithm for GC treatment (Morabito,Carillio and Longo 2009).

2. Determine the standard treatment elements and probability of receiving specific treatment components (Table 5-9).
3. Aggregate the cost stream to obtain expected incremental cost of GC (Table 5-10)

Expert opinion of Dr. Dan Yock Young, an expert in clinical gastroenterology and cost-effectiveness modeling at the NUH Singapore, was sought to ascertain treatment components for each clinical stage. Hospital charges were used to estimate the cost of treatment elements. The post-treatment follow-up costs encompassed all expenditures after initial diagnosis and aggressive treatment

Table 5-9. Algorithm of stage specific gastric cancer treatment

Stage	Medical Components	Medical Service Mix
Stage 1	Endoscopic mucosal resection/ Endoscopic submucosa dissection	30%
	Total/subtotal gastrectomy	70%
Stage 2a	Total/subtotal gastrectomy	60%
Stage 2b	Total/subtotal gastrectomy + chemotherapy	40%
Stage 3	Total/subtotal gastrectomy + chemotherapy	100%
Stage 4	Basic support care	30%
	Bypass surgery + chemotherapy	30%
	Chemotherapy	40%

Table 5-10. Diagnostic cost and treatment cost by clinical stage

Components	Cost $ Mean (Range)	Reference
Diagnosis & staging for program detected GC cases*	740 (660 - 820)	
Diagnosis & staging for clinically diagnosed GC cases †	1155 (960-1440)	
Cost of treatment		
Stage 1	20000 (10000 - 40000)	(Hospital Case mix Records 2012)
Stage 2	27200 (13600 - 54400)	Expert opinion
Stage 3	38000 (19000 - 76000)	
Stage 4	15500 (7800 - 31100)	
Post-treatment follow-up	955 (900-1300)	

CT, computed tomography; CXR, chest radiograph; ICU, intensive care unit
** CT scan/CXR/ultrasound/blood test*
† OGD / biopsy / blood tests / ultrasound / CT

As cost data followed right-skewed distributions (Thompson and Barber 2000), base case estimates were halved and doubled to produce the range (Chang et al. 2012). Costs were expressed as 2012 constant United States dollar ($) at an annual average exchange rate of 1.25 Singapore dollars.

5.4.5.3 Cost assignment in TreeAge program

The costs were assigned to the clinical events where medical resources were consumed. As shown in the Markov tree simulating surveillance pathway of high risk subjects (Figure 5-24), the follow-up OGD cost was assigned at step 1, the cost for confirmative tests was assigned at step 2, the stage-specific treatment cost was assigned at step 3. As the model calculated the incremental cost, the cost for basic medical care and the terminal care prior to death was not taken into account. Thus no costs were assigned on the branches *"Death for other reasons"* and *"OGD negative"* representing high risk subjects not yet developing GC.

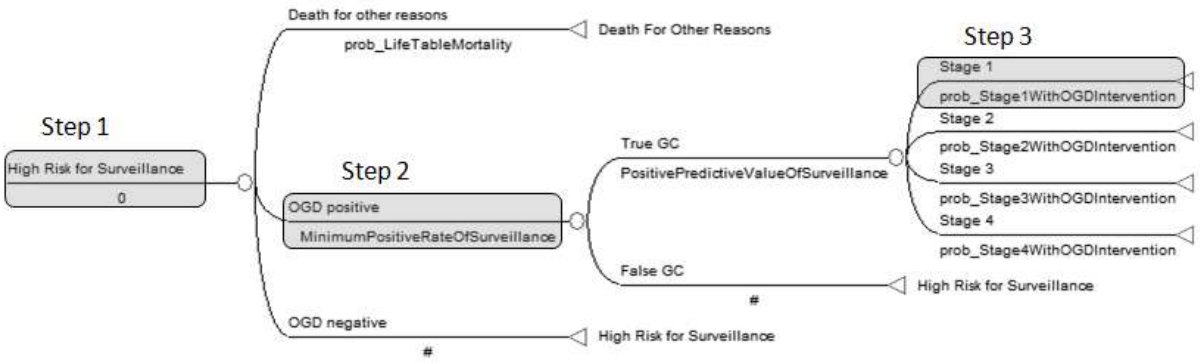


Figure 5-24. Cost assignment in Markov trees

5.4.6 Utility

Health states free of GC in our model are assumed to be in full health, i.e., utility is 1 for these states. The death state is associated with a utility of zero. For GC patients in different clinical stages, their utility scores have been measured in **CHAPTER IV: QUALITY OF LIFE OF PATIENTS WITH**

GASTRIC CANCER. We used mean EQ-5D score of each clinical stage, which is anchored between 0 (death) and 1 (full health), as stage-specific utility. Therefore in our model, utility for cancer, death and full health states are in coherence with each other. The stage-specific utilities are summarized in Table 5-11.

In conformity to our assumption that, after diagnosis and initial treatment, GC patients remain stable until death, the utility of GC patients are constant until patient's death. Considering the negative effect on the patients' quality of life due to surgery or chemotherapy, we assumed a 6-month period when the utility is only half of that when the disease is stable (Munene et al. 2012). For both death due to GC or other reasons, we did not account for the utility deterioration three months before death (Environmental Protection Agency USA 2000).

Table 5-11. Stage-specific utility of gastric cancer patients

Clinical Stage	Mean (95% CI)	Percentile					Disutility*
		10	25	50	75	90	
Stage 1	0.88 (0.77-0.98)	0.60	0.80	1	1	1	- 0.28
Stage 2	0.86 (0.73 - 0.99)	0.46	0.71	1	1	1	- 0.29
Stage 3	0.77 (0.58 - 0.95)	0.09	0.74	0.81	1	1	- 0.31
Stage 4	0.68 (0.51 - 0.84)	0.12	0.46	0.80	1	1	- 0.33

** 6-month period when QoL deteriorates due to initial diagnosis and treatment*

CHAPTER VI. COST EFFECTIVENESS ANALYSIS - MODEL VALIDATION & PROJECTIONS

In Chapter V, we presented the detailed process of building a Markov model. The limitations and advantages were explained about using different data and assumptions. This practice meets the requirement for transparency and thus technically validates our model to a certain degree (Eddy et al. 2012). For a model to provide useful qualitative or quantitative information, an official validation process is necessary and important whereby the model outputs are compared with the existing data for the consistency between them. Due to practical constraints, we conducted only the internal validation in the present project.

6.1 Internal Validation of the Markov Model

Regarding model validation, one has to take note that discrepancies between model outputs and the existing data are inevitable. In the case of our models, the primary discrepancy lies in the study design. We built cohort-based Markov models to simulate the target population of Singapore Chinese at 50-69 years old. Such a model assumes that the population modeled is a static and homogeneous cohort, that is, the population will not increase or decrease due to reasons other than death either from GC or for other reasons. However, the real residential population in Singapore, which includes citizens and permanent residents, is a dynamic cohort with a fluctuating population size in response to government migration policies. Our target population, in particular, increased every year for the past two decades (Department of Statistics Singapore 2012). Therefore, even if our models are perfect in modeling a static cohort representing the target population, there will still be some discrepancies between model outputs and the existing data.

Internal validation was conducted to examine how well our models represent the target population in terms of epidemiological profile. The two most important variables are GC incidence and all-cause mortality. The TreeAge structures in

Figure 5-7. Markov Model for the no OGD intervention,

Figure 5-8. Markov Model for the screening strategy

Figure 5-9. Markov Model for the surveillance strategy

were adapted to calculate the age-specific GC incidences and all-cause mortality for validation against the population data reported by Singapore Cancer Registry and Department of Statistics Singapore.

6.1.1 Validation of gastric cancer incidence

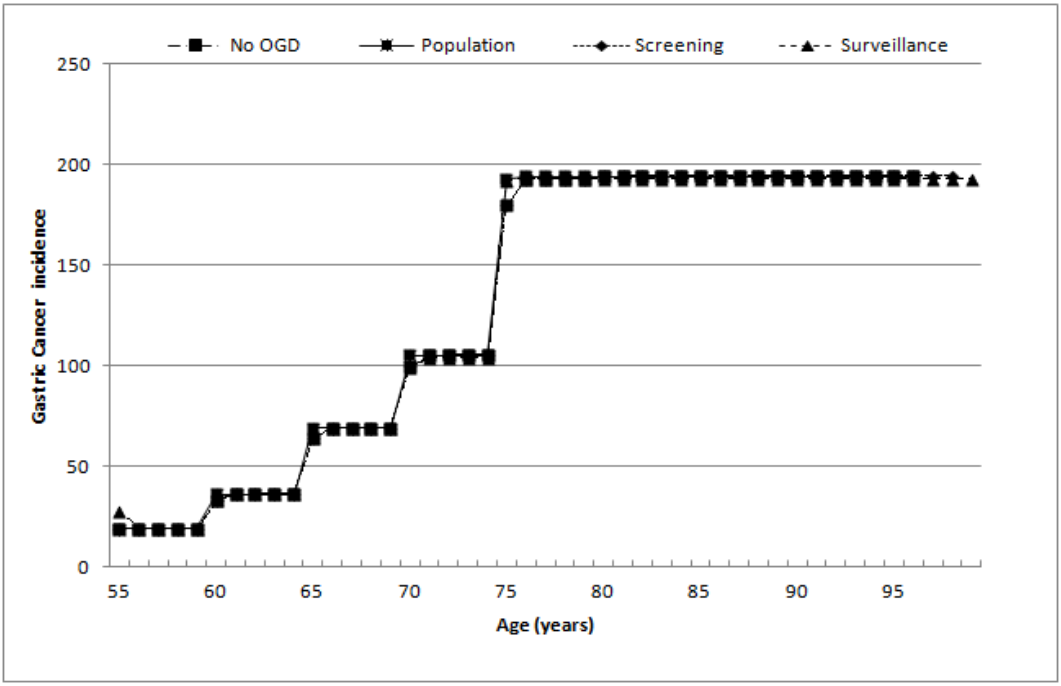


Figure 6-1. Age-specific gastric cancer incidence of Singapore Chinese

As shown in Figure 6-1, the incidences projected by the Markov models for the no OGD intervention, screening and surveillance strategies are almost same as the original data inputted with the four incidence curves overlapping with each other. This observation is in line with the theory that the screening and surveillance strategies are not supposed to affect GC development. It also indicates that

our models did not misestimate the GC incidences for each strategy. The chances are rare that the benefit of a screening or surveillance program would be biased by miscomputation of GC incidences.

6.1.2 Validation of all-cause mortality

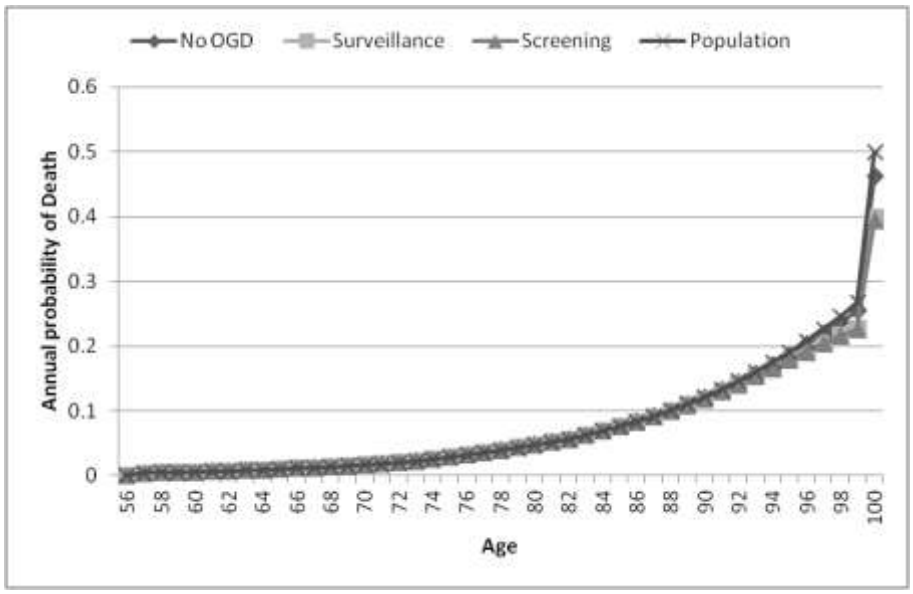


Figure 6-2. Age-specific all-cause mortality of Singapore Chinese (original vs. model estimates)

Age-specific mortalities were estimated by the three models and compared with the Life Table of the Singaporean Chinese. As in Figure 6-2, before the age of 70 years, the four mortality curves almost overlap with each other. Differences begin to appear after the age of 70 years with the screening and surveillance curves running below those of the Life Table and no OGD intervention, indicating the survival benefit due to these two preventive measures. However, the differences are subtle before the age of 82 years, which is the life expectancy of an average Singaporean Chinese. After that age threshold, the mortality reduction from the screening and surveillance strategy becomes more pronounced until the whole cohort dies.

The fact that screening or surveillance strategies exhibit a survival benefit late in life is clinically plausible. This phenomenon is referred to as the “time-lag” effect of preventive measures in public

health. From an epidemiological point of view, GC-specific mortality accounts for barely 2% of all-cause mortality in Singapore (Singapore Cancer Registry Committee 2010) which is the upper bound for mortality reduction potential due to a preventive strategy. This proportion is too small to immediately demonstrate the survival benefit by any preventive measure on a population level.

6.2 Model Outputs in the Base-Case Scenario

6.2.1 Cohort analysis

For the target population of 50-69 year old Chinese, the overall lifetime risk of dying from GC was 2.62%. Surveillance would reduce this risk by 33% to 1.76% while screening would further reduce it to 1.73% (Table 6-1). Given the target population size of 712,600 (Department of Statistics Singapore 2012), the screening strategy would avoid 6342 deaths due to GC (male 3,787 and female 2,403) and surveillance would save 6128 lives from GC (male 3,859 and female 2,367). To realize these benefits, the surveillance strategy required 4.4 OGD examinations per person over a lifetime, which was approximately one third of OGD examinations (n=13.5 per person) required for the screening strategy.

Table 6-1. Reduction in gastric cancer related death by the surveillance and screening strategies

Population	Lifetime risk of death	No OGD	Surveillance	Screening
Whole cohort	Other reasons (%)	96.65	97.28	97.32
n=712,600	Gastric cancer (%)	2.62	1.76	1.73
	GC deaths averted (n)		6,128	6,342
Male	Other reasons (%)	95.94	96.73	96.70
n=354,000	Gastric cancer (%)	3.38	2.29	2.31
	GC deaths averted (n)		3,859	3,787
Female	Other reasons (%)	97.36	97.80	97.77
n=358,600	Gastric cancer (%)	1.92	1.26	1.25
	GC deaths averted (n)		2,367	2,403

6.2.2 Cost-effectiveness analysis

Comparisons of the cost-effectiveness of the three strategies are illustrated in Figure 6-3. Under the reference strategy of no OGD intervention, each subject would experience 18.22 QALYs at the cost of $542. Focused surveillance in high risk subjects would acquire 0.0665 more QALYs at an additional cost of $1,998, resulting in an ICER of $30,033/QALY. Population screening compared to surveillance would cost $3,170 more with an additional benefit of 0.0075 QALYs. This would yield an ICER of up to $421,247 /QALY, more than nine times the WTP threshold of $46,200/QALY. Based on ICERs associated with the two competing strategies, surveillance would be considered cost-effective in Singapore. Dominance or extended dominance, when one strategy is less effective but more expensive than another strategy or combination of strategies, was not exhibited in the comparisons.

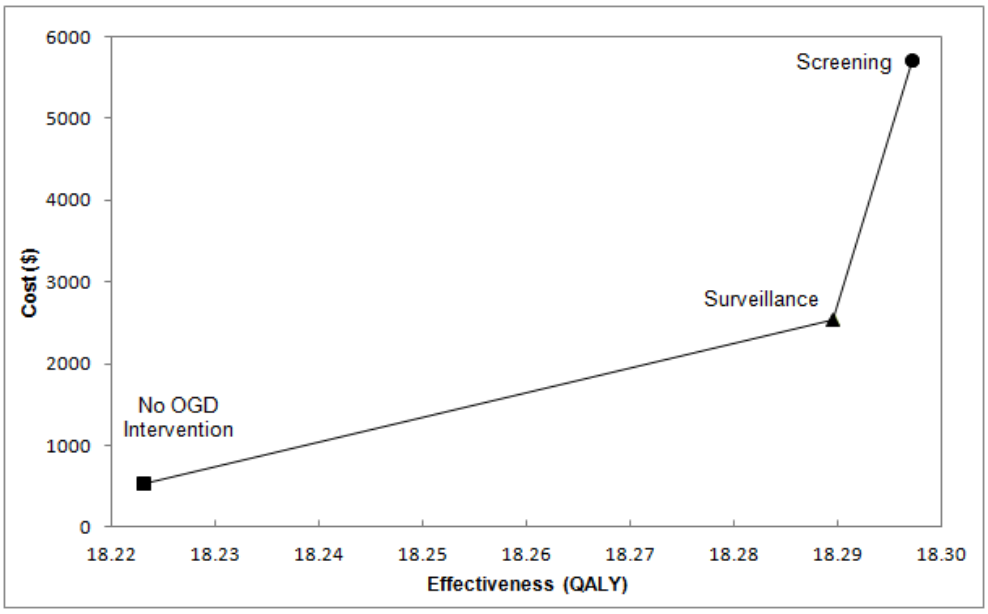


Figure 6-3. Comparing the cost effectiveness of no OGD intervention, screening and surveillance strategies

6.2.3 Heterogeneity in cost effectiveness

It is of public health significance to explore the heterogeneity in the cost effectiveness of screening and surveillance given different baseline GC risk and background mortality. Table 6-2 compares the cost, effectiveness and ICERs of screening and surveillance for age and gender subpopulations. Compared with the usual practice of no OGD intervention, surveillance is cost-effective with ICERs below $46,200/QALY for all subgroups except for females below 60 years old. The screening strategy is not cost-effective relative to surveillance as its ICERs are far more than $46,200/QALY and are not stable. As expected theoretically, males featured by higher GC risk and background mortality (Department of Statistics Singapore 2012; Singapore Cancer Registry Committee 2012) are associated with lower ICERs than those for females by a ratio of 2 to 5. Starting surveillance at an older age appears more cost-effective than at a younger age as shown by the negative relationship between cohort age and ICERs.

For the reference strategy, the older age groups have incurred more cost than younger age groups, despite their shorter life expectancy (Table 6-2, column 2 and 3). This finding is seemingly count-intuitive and is caused by discounting the future costs in the Markov model, a practice recommended for all economic evaluations. In simulating lifetime experience, future costs will be discounted every year to the present monetary value. Older age cohorts, who have much higher GC incidence, consume far more resources for treatment and post-treatment follow-up than younger age groups at the beginning. Therefore, the cost incurred at present is high. Although more money would be spent on younger age groups later on, it is discounted every year. Setting a discount rate as 0 will make younger age groups accumulate more cost than older age groups by a small margin. For the surveillance or screening strategies, follow-up OGD costs a larger amount of money every year so discounting does not show its effect.

Table 6-2. Heterogeneity of the three strategies by age and gender

	No OGD Intervention		Surveillance			Screening		
	Cost ($)	**Utility (QALY)**	**Cost ($)**	**Utility (QALY)**	**ICERs**	**Cost ($)**	**Utility (QALY)**	**ICERs**
Whole cohort								
Overall	546	18.223	2,820	18.290	34,187	6,764	18.297	84,027
50-54	478	20.487	2,952	20.549	39,761	7,464	20.552	116,433
55-59	538	18.617	2,839	18.687	33,046	6,890	18.690	90,743
60-64	596	16.579	2,707	16.656	27,489	6,256	16.659	70,750
65-69	636	14.431	2,548	14.512	23,470	5,566	14.515	61,625
Male								
Overall	717	17.232	2,905	17.326	23,201	6,618	17.340	54,437
50-54	625	19.573	3,019	19.660	27,668	7,317	19.669	66,920
55-59	710	17.636	2,923	17.734	22,535	6,747	17.744	60,370
60-64	789	15.544	2,808	15.653	18,502	6,122	15.665	44,442
65-69	850	13.368	2,666	13.485	15,531	5,443	13.494	38,275
Female								
Overall	389	19.141	2,749	19.187	50,852	6,910	19.191	130,160
50-54	343	21.351	2,900	21.395	57,693	7,615	21.396	145,440
55-59	382	19.529	2,772	19.578	49,156	7,035	19.578	133,060
60-64	423	17.517	2,627	17.570	41,287	6,392	17.571	119,380
65-69	451	15.359	2,453	15.416	35,276	5,686	15.415	104,700

ICER; Incremental cost effectiveness ratio. The unit for ICER is $/QALY.

6.3 Deterministic Sensitivity Analysis

We compared outcomes of two scenarios when implementing the screening strategy. One scenario was that the whole target population undertook screening OGDs in alternative years, therefore the screening service would be provided intermittently. The other was that, as specified in **Section 5.2.3.1, Endoscopic screening**, two halves of the target population undertook screening OGDs in turn so that screening service would be provided in a continuous way. The second scenario has shown better cost-effectiveness than the former.

One-way sensitivity analysis was also applied to identify the factors with significant impact on the model results. The range for each parameter was based on the upper and lower bounds of biological plausibility as reported in the literature. We analyzed net health benefit (NHB) of each Markov model to quantify the impact of every parameter. Sensitivity analysis also helped to identify the possible thresholds of each parameter across which the choice of optimal strategy would have changed. Another function of deterministic sensitivity analysis is to examine the model assumptions against the current clinical and economic understanding. We did not run sensitivity analyses on GC incidence because its variations have been well represented by specific values across age and gender subpopulations.

In none of scenarios during the univariate sensitivity analysis was screening the cost-effective strategy. The optimal strategy is a choice between surveillance and no OGD intervention. The base-case finding that surveillance is cost-effective in the Singapore healthcare system is quite robust to most parameters populating the model. If the range of a parameter is able to cause a 0.2 QALY change in surveillance NHB, the parameter was considered influential to our model.

Sensitivity analysis identified nine such parameters which are listed in deceasing order of magnitude in Table 6-3. As anticipated *a priori*, the discount rate, age of starting surveillance, cost of follow-up OGD and baseline OGD, and proportion of program cost are negatively related to surveillance NHB, while the OR of high risk subjects, prevalence of premalignant lesions and utility of GC Stage 1 have positive correlations with surveillance. These relationships are very useful in customizing an actual program in consideration of the practical limitations.

Table 6-3. Parameters impactful on net health benefit of surveillance strategy identified by sensitivity analysis

Input parameters	Range	Variation of Surveillance NHB	Relationship with Surveillance NHB	Threshold
Discount rate (%)	0-5	12.64	Negative	
Age (years)	50-69	7.68	Negative	-
Willingness-to-pay ($1000/QALY)	15-100	0.15	Positive	>30.3
Odds ratio of high risk subjects	2.4-21.5	0.09	Positive	> 3.11
Program cost Proportion (%)	20-80	0.06	Negative	< 67
Utility of GC Stage 1	0.6-1	0.05	Positive	> 0.63
Cost of follow-up OGD ($)	170-680	0.04	Negative	< 624
Prevalence of premalignancy (%)	6.8-48.2	0.03	Positive	-
OGD cost at baseline ($)	350-1400	0.02	Negative	-

6.3.1 Discount Rate

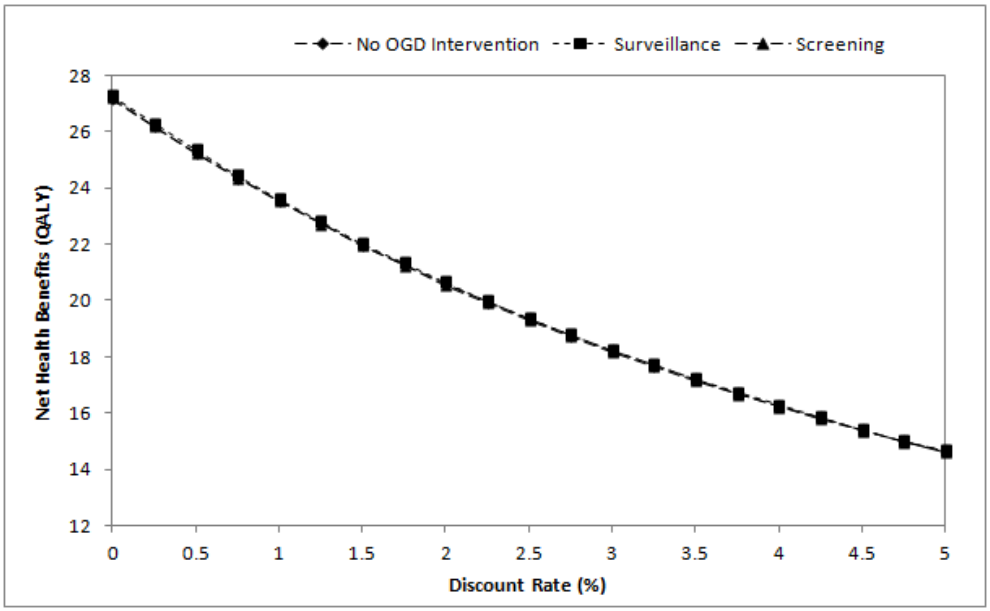


Figure 6-4. Net Health Benefit variation across the range of the discount rate

Discount rate is an economic parameter gauging the time-preference of Singapore society. It appears to be the most influential parameter for the model. Varying the discount rate from 0 to 5% would cause a reduction of approximately 50% of NHBs for all the three strategies. Although NHB changes dramatically by the discounting, the choice of optimal strategy is robust to the discount rates commonly used in the literature.

6.3.2 Age of starting OGD follow-up

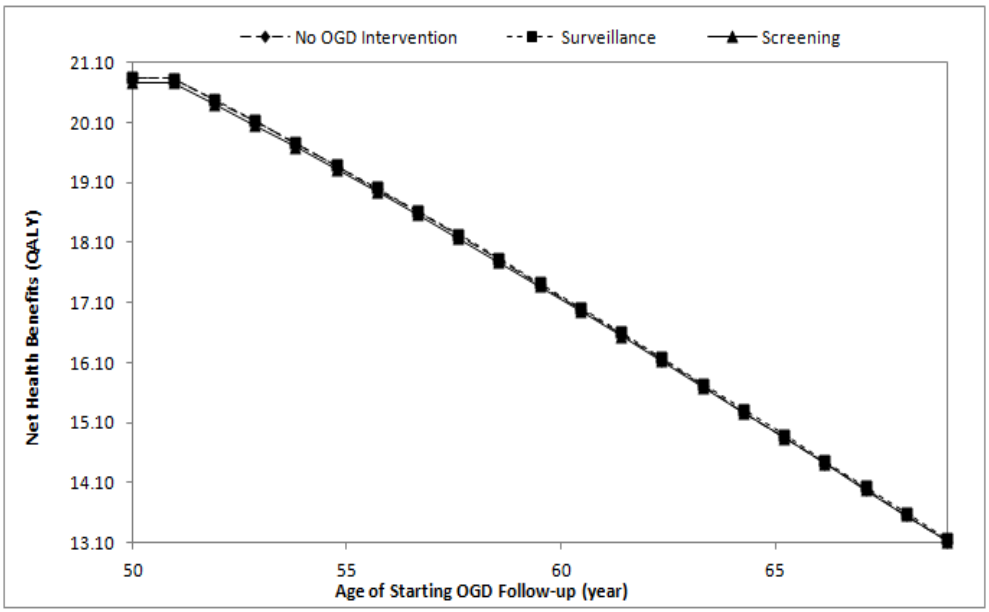


Figure 6-5. Net Health Benefit variation across the range of age starting follow-up

Age at which OGD follow-up starts is the second most influential factor. The negative relationship between NHBs and starting age is expected which means starting the intervention at an earlier time can harvest more healthy years. Our model projected that an individual undertaking OGD examination at the age of 50 years would generate 7.68 QALYs more than when he undertakes it at age of 69 years for the surveillance strategy. However, this huge variation in NHBs associated with the starting age does not change the choice of optimal strategy which is the surveillance strategy in Singapore Chinese.

6.3.3 Willingness-To-Pay

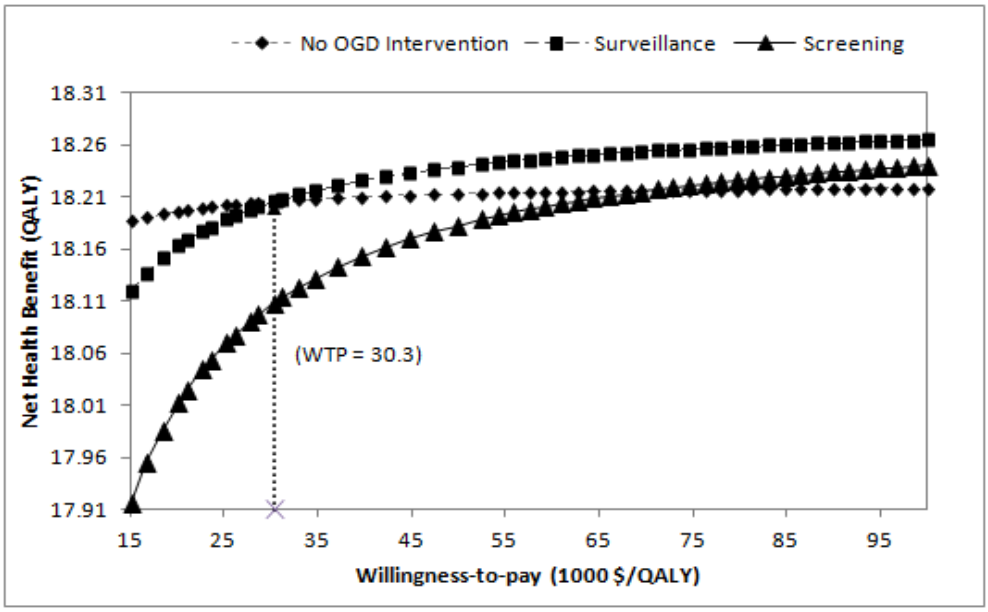


Figure 6-6. Net Health Benefit variation across the range of willingness-to-pay

WTP is another economic parameter which is Singapore-specific in our model. Unlike discount rate and starting age that affect all the three strategies equally, WTP exerts different influences in terms of NHB generation (Figure 6-6). As the WTP grows, indicating that a healthcare system is willing to pay more for health, both surveillance and screening would create more and more health years with the latter at a faster pace. However, the increase of WTP has little effect on the reference strategy. Comparing surveillance with no OGD intervention, a threshold of 30,300 $/QALY was identified above which surveillance becomes the cost-effective strategy over no OGD intervention.

6.3.4 Odds ratio

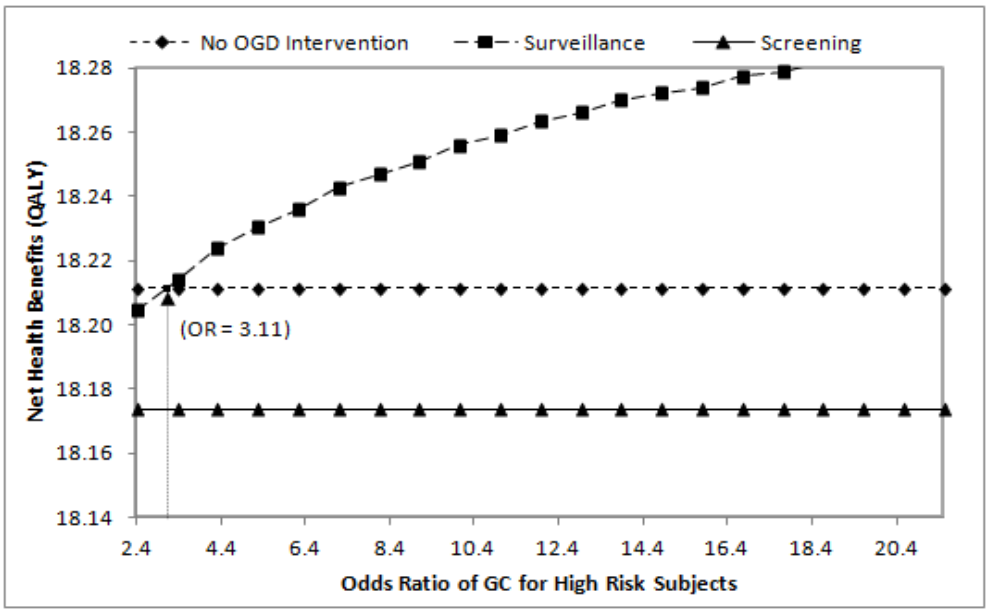


Figure 6-7. Net Health Benefit variation across the range of odds ratio of high risk subjects in the surveillance strategy

Odds ratio (OR) was used to differentiate high and low risk subjects from the target population for the surveillance strategy. The OR ranges widely from 2.4 to 21.5 to represent various precancerous lesions from chronic atrophic gastritis to gastric mucosa dysplasia (Watabe et al. 2005). Figure 6-7 displays an upward trend of NHB with increasing ORs which means that the surveillance strategy works more efficiently for more susceptible subpopulations. These results are biologically expected. As OR is not one of the input parameters for no OGD intervention and screening, their NHBs remain constant. An OR of 3.11, the GC risk of patients with atrophic gastritis, was discovered to be the threshold above which surveillance is more cost-effective than no OGD intervention.

6.3.5 Program cost

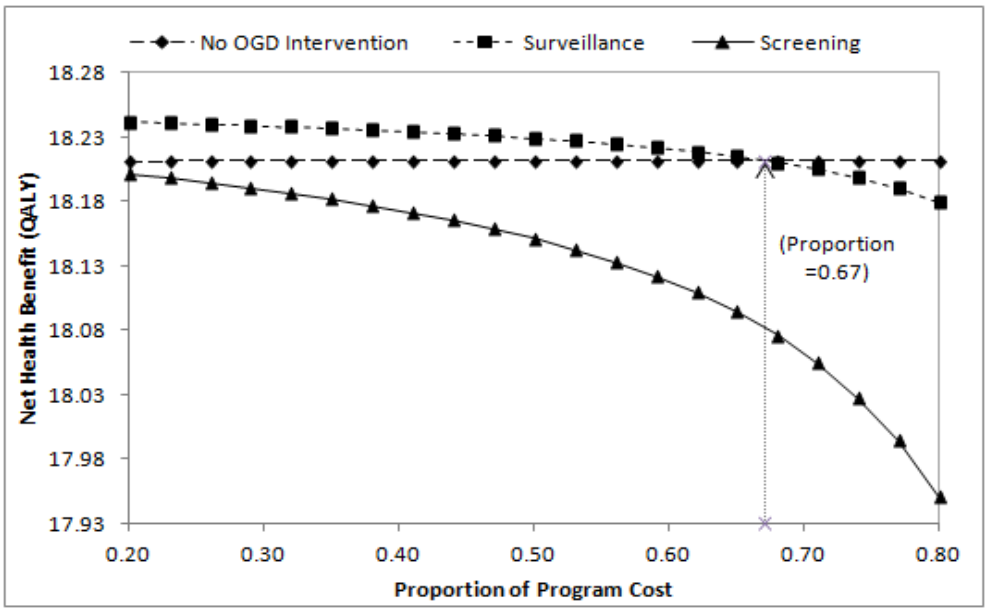


Figure 6-8. Net Health Benefit variation across the range of proportion of program cost of operational cost

Program cost measures the resources used in supporting activities to deliver the essential clinical services, which are OGD examinations in our study. From the perspective of program evaluation, program cost serves as an indicator of the operating efficiency of a program. Judging by definition, less program cost means better operating efficiency. Our model represents the program cost as a proportion of total operational cost.

As shown in Figure 6-8, program cost is able to influence both screening and surveillance strategies. The screening strategy is more sensitive to program cost than the surveillance strategy because it needs to carry out far more follow-up OGDs. As expected theoretically, a higher proportion is associated with a lower NHB. Our model further suggested a threshold of 67% for a surveillance program to be considered cost-effective in Singapore.

6.3.6 Utility of gastric cancer stage 1

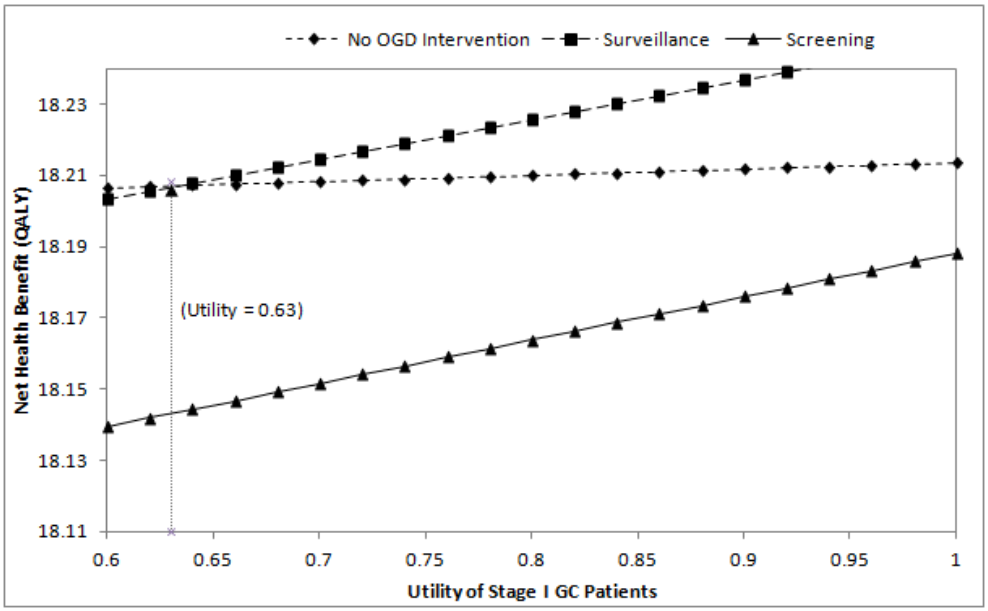


Figure 6-9. NHB variation across the range of utility of Stage 1 gastric cancer patients

Utility of Stage 1 GC patients reflects the clinical outcome of managing early GC cases in Singapore. Sensitivity analysis (Figure 6-9) demonstrates a positive linear relationship between the utility of early GC patients and NHBs of the three strategies. This positive relationship validates our model in the sense that better clinical outcomes lead to more health gain from strategies evaluated. It is expected that the slope for the no OGD intervention strategy is the lowest; because the surveillance and screening strategies are supposed to produce more Stage 1 patients than no OGD intervention. Surveillance is the cost-effective strategy if the quality of life of Stage 1 GC patients reaches 0.63.

6.3.7 Cost of follow-up OGD

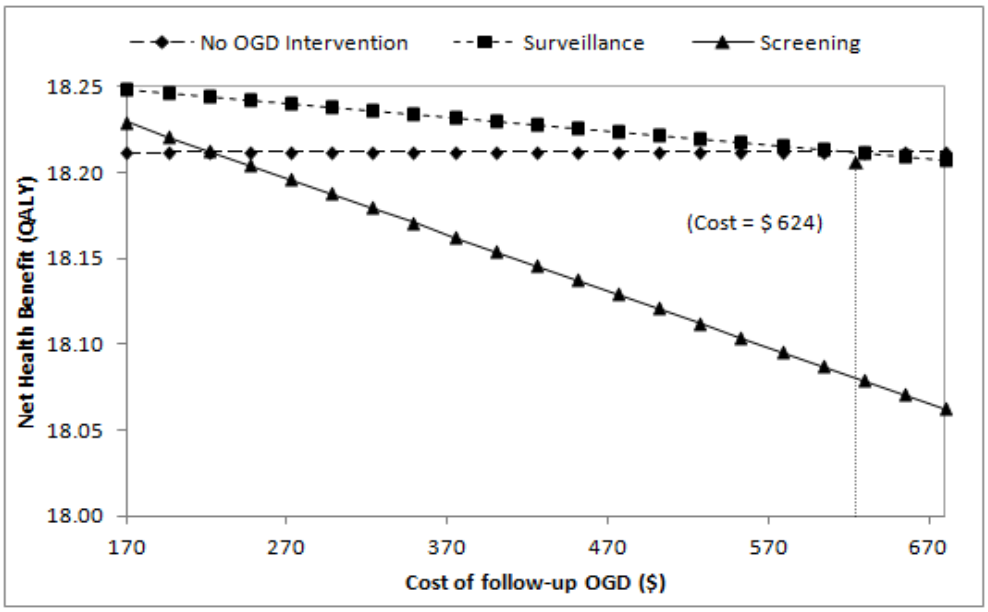


Figure 6-10. Net Health Benefit variation across the range of follow-up OGD cost

As shown in Figure 6-10, follow-up OGD cost negatively influences the model output of the surveillance and screening strategies. The slope for the screening strategy is steeper than that for surveillance implying that the former was more sensitive to follow-up OGD cost than the latter. This is due to the fact that the screening strategy needs more follow-up OGDs than the surveillance by examining half of the target population ever year (**5.2.3.1: Endoscopic screening).** Regarding the choice of optimal strategy, surveillance would be cost-effective if follow-up OGD price can be provided at the cost below $624 in Singapore.

6.3.8 Cost of baseline OGD

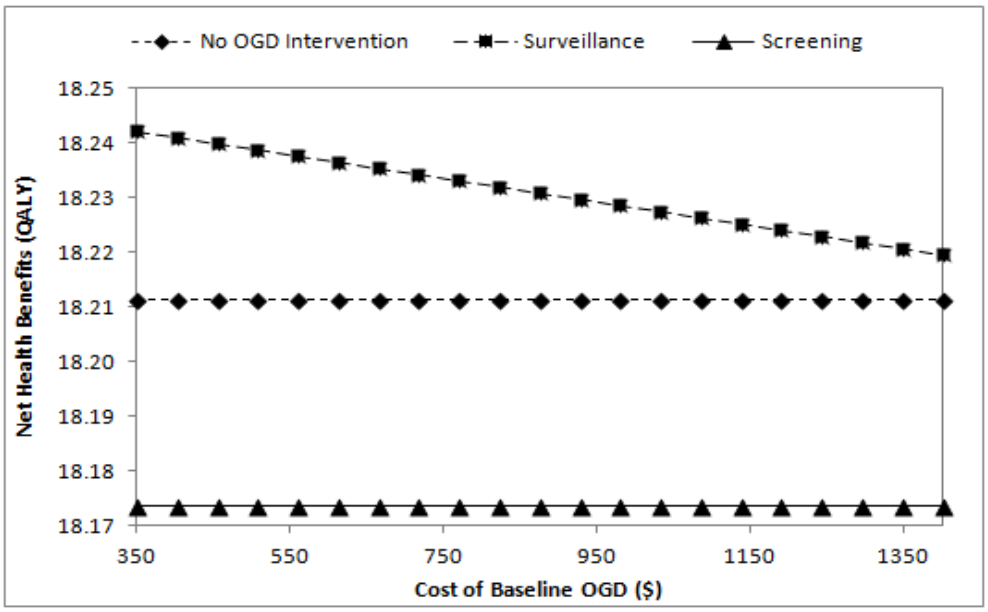


Figure 6-11. Net Health Benefit variation across the range of baseline OGD cost of the surveillance strategy

Baseline OGD was used in the surveillance strategy to categorize the target population. As shown in Figure 6-11, given the fixed WTP of $46,200/QALY, increasing the baseline OGD cost will reduce QALYs produced by the surveillance. Its advantage over no OGD intervention and screening shrinks. Covering the full range of baseline OGD price from $350 to $ 1400, surveillance persists as the cost-effective strategy.

6.3.9 Prevalence of precancerous gastric lesions

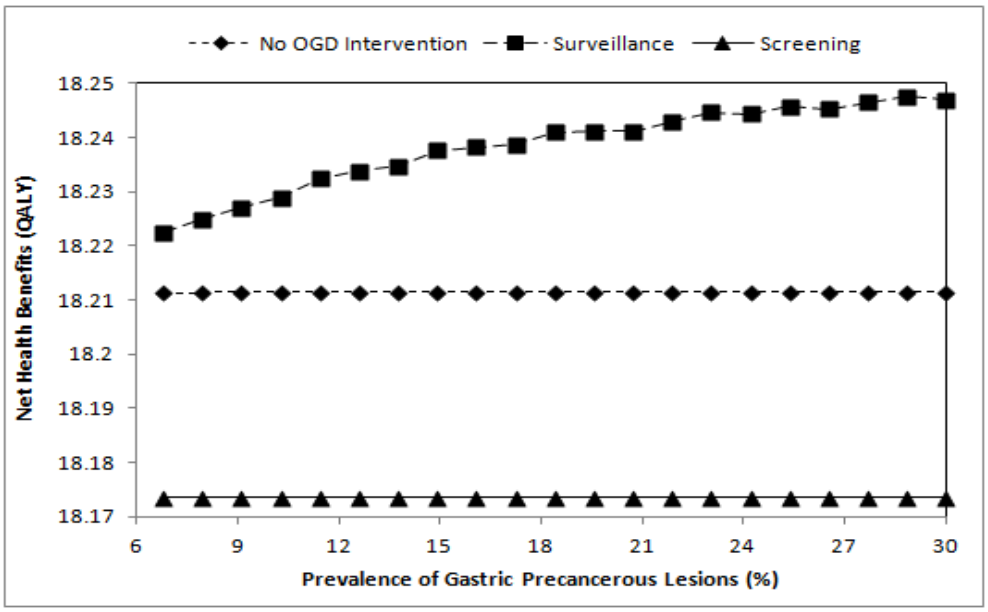


Figure 6-12: Net Health Benefit variation across the range of prevalence of gastric precancerous lesions

Variation of the prevalence of gastric precancerous lesions represents the fact that the potential burden by GC disease is different in different groups. Within the range of 6.8% to 27%, NHB from the surveillance strategy increases with the growing prevalence of precancerous lesions (Figure 6-12). This upward trend highlights that the surveillance strategy should be preferably implemented in a population with higher GC burden.

6.4 Probabilistic Sensitivity Analysis

To assess the influence of uncertainties associated with the parameter estimates, we conducted a probabilistic sensitivity analysis (PSA) with 1000 Monte Carlo simulations by sampling distributions of nine parameters individually or collectively (Table 6-4). We chose not to analyze all parameters for two reasons, (1) it is unnecessary to introduce too many uncertainties in the model; and (2) parameters like proportion of program cost and cost of follow-up OGD and GC treatment are arbitrary and their estimates therefore are not associated with sampling error.

The nine parameters chosen were the prevalence of precancerous lesions, the OR for GC of high risk relative to low risk, utility scores of the four clinical stages, and stage compositions of GC cases detected with or without OGD intervention. The Bayesian posterior distributions were assigned to these parameters after examining the statistical properties of the point estimates. The individual variation of age starting OGD follow-up was reflected by the actual age distribution of the target population at baseline. The possibility of being the cost-effective strategy given different WTPs was plotted as a cost-effectiveness acceptability curve (CEAC) for the three strategies.

Table 6-4. Distributions assigned to parameters in probabilistic sensitivity analysis

Input Variables	Type of Distribution	Mean (S.D)
Utility Score		
Stage 1	Gamma*	0.88 (0.05)
Stage 2	Gamma*	0.86 (0.07)
Stage 3	Gamma*	0.77 (0.10)
Stage 4	Gamma*	0.68 (0.08)
Odds ratio†	LogNormal*	6.00 (2.46)
Prevalence of premalignant gastric lesions (%)	Beta*	13.5 (6.75)
Stage distribution of GC cases(Stage 1:2:3:4)		
Population with OGD follow-up	Dirichlet	85%:4%:8%:3%
Population without OGD follow-up	Dirichlet	7%:17%:33%:43%
Age of starting OGD	Actual distribution	

* *Methods of moments; S.D: standard deviation*
† *Odds ratio of GC in high risk group relative to low risk group*

6.4.1 Utility of gastric cancer patients at each clinical stage

Utility scores are special parameters in terms of their range. Theoretically, it can assume any value from negative infinity (worse than death) to the natural upper constraint of 1 (full health). To fit utility score in PSA, a simple transformation 1-Utility is employed so that the derived variable 1-Utility follows a gamma distribution with a range of 0 to positive infinity.

Utility information is usually provided by a quality of life study. The stage-specific EQ-5D scores in **CHAPTER IV: QUALITY OF LIFE OF PATIENTS WITH GASTRIC CANCER** were used to represent the utility of Singapore Chinese patients with GC in our model. The two parameters for gamma distributions (α, λ) were estimated by methods of moments approach using means and standard deviations of EQ-5D for each GC stage.

6.4.1.1 Distributions sampled in probabilistic sensitivity analysis for utility scores of gastric cancer patients at four clinical stages.

Figure 6-13, Figure 6-14, Figure 6-15 and Figure 6-16 below display the gamma distributions representing the randomness associated with utility estimates for each GC stage.

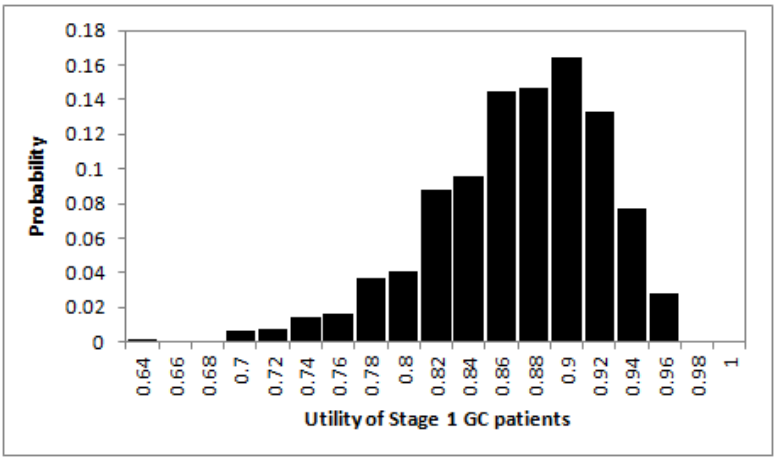


Figure 6-13. Simulated Gamma (310, 352) of the utility of Stage 1 patients

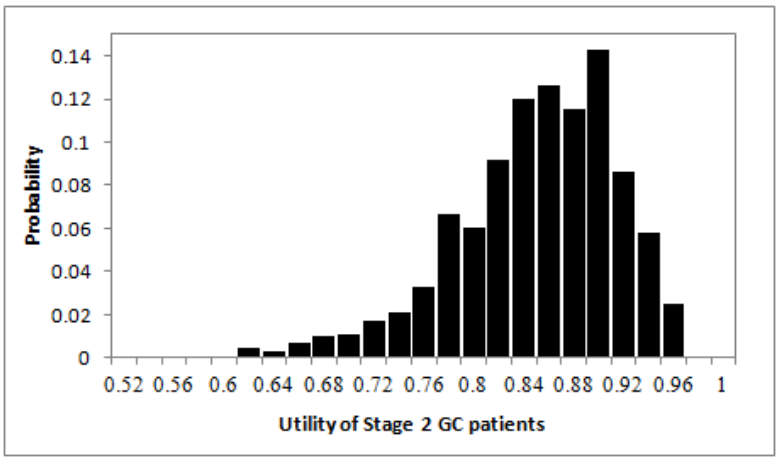


Figure 6-14. Simulated Gamma (151, 176) of the utility of Stage 2 patients

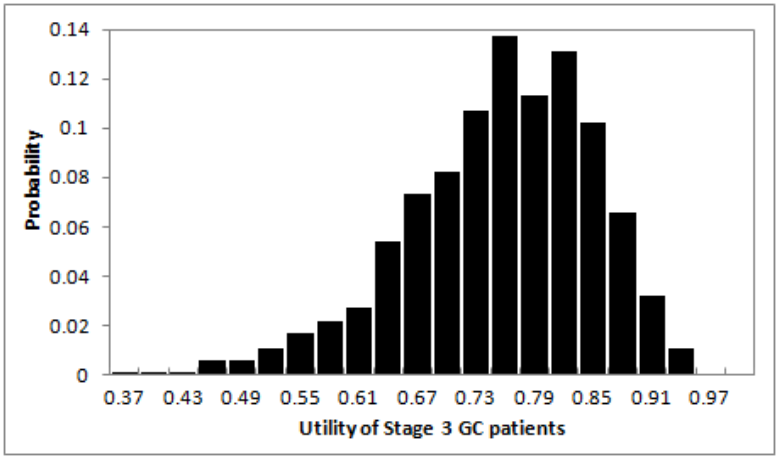


Figure 6-15. Simulated Gamma (60, 77) of the utility of Stage 3 patients

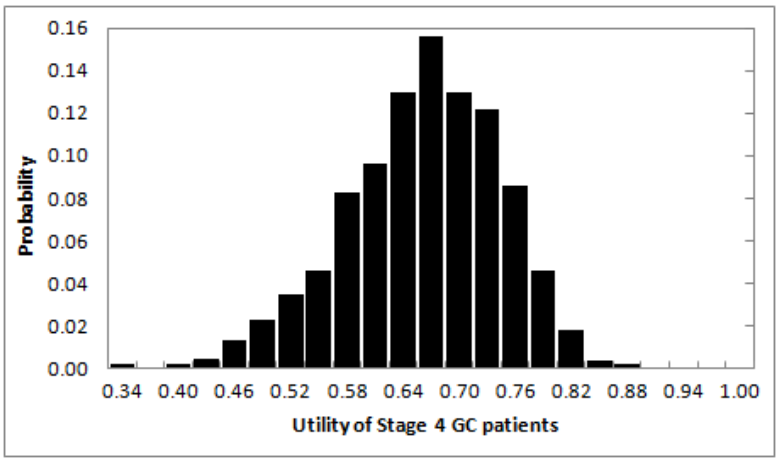


Figure 6-16. Simulated Gamma (72, 106) of the utility of Stage 4 patients

As explained in the beginning of this section, the above distributions are not EQ-5D distributions observed in **CHAPTER IV: QUALITY OF LIFE OF PATIENTS WITH GASTRIC CANCER**, but theoretical distributions generated by the TreeAge program based on the EQ-5D results.

6.4.1.2 Cost-effectiveness acceptance curves for individual distributions of the four clinical stages

The CEACs derived by PSA sampling individual distributions are presented for each clinical stage. After incorporating the uncertainty surounding the utilities of Stage 2, Stage 3 and Stage 4 GC patients, the probability of surveillance being the cost-effective strategy is one at the Singapore-specific WTP of 46,200 $/QALY (vertical line in Figure 6-17, Figure 6-18 and Figure 6-19). This probability is slightly lower at 99.90% if the model accounts for only the uncertainty surounding the utility of Stage 1 GC patients (Figure 6-20).

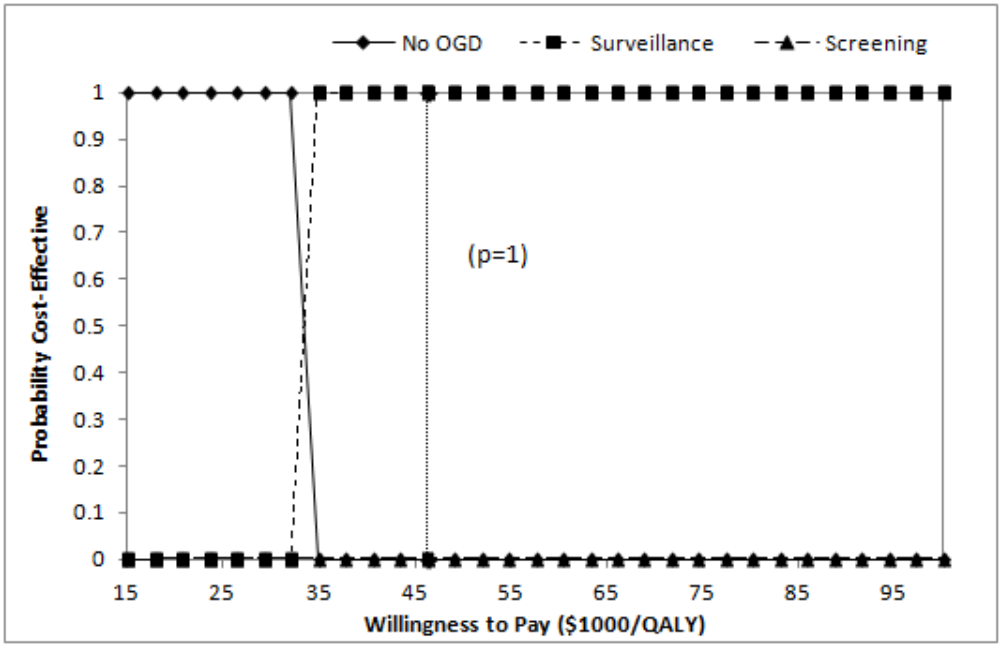


Figure 6-17. Probability of being cost-effective of the three strategies when accounting for uncertainties surrounding the utility of Stage 2 patients

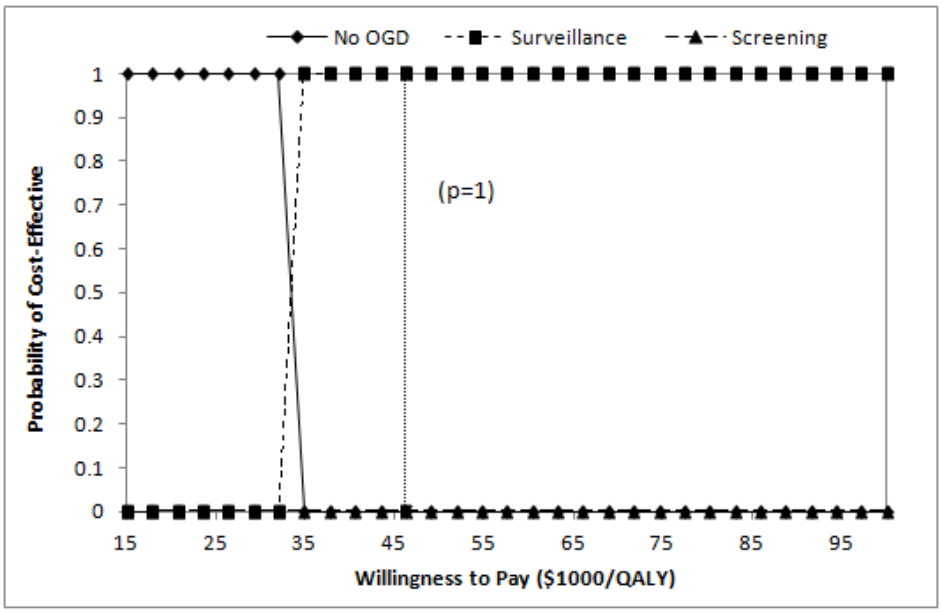


Figure 6-18. Probability of being cost-effective of the three strategies when accounting for uncertainties surrounding the utility of Stage 3 patients

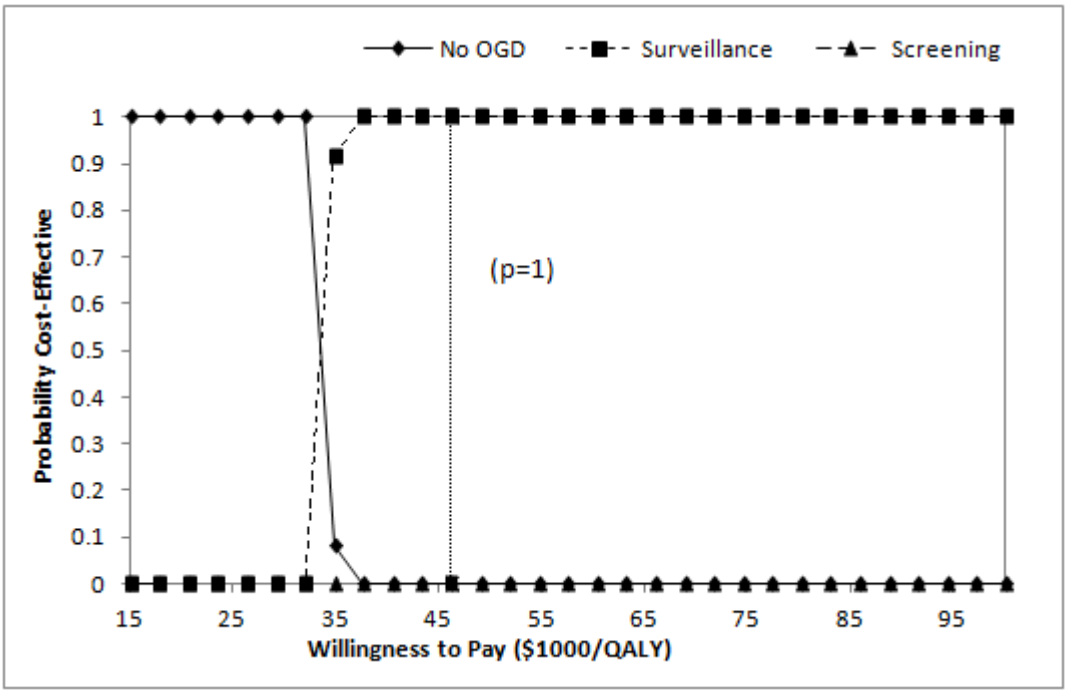


Figure 6-19. Probability of being cost-effective of three strategies when accounting for uncertainties surrounding the utility of Stage 4 patients

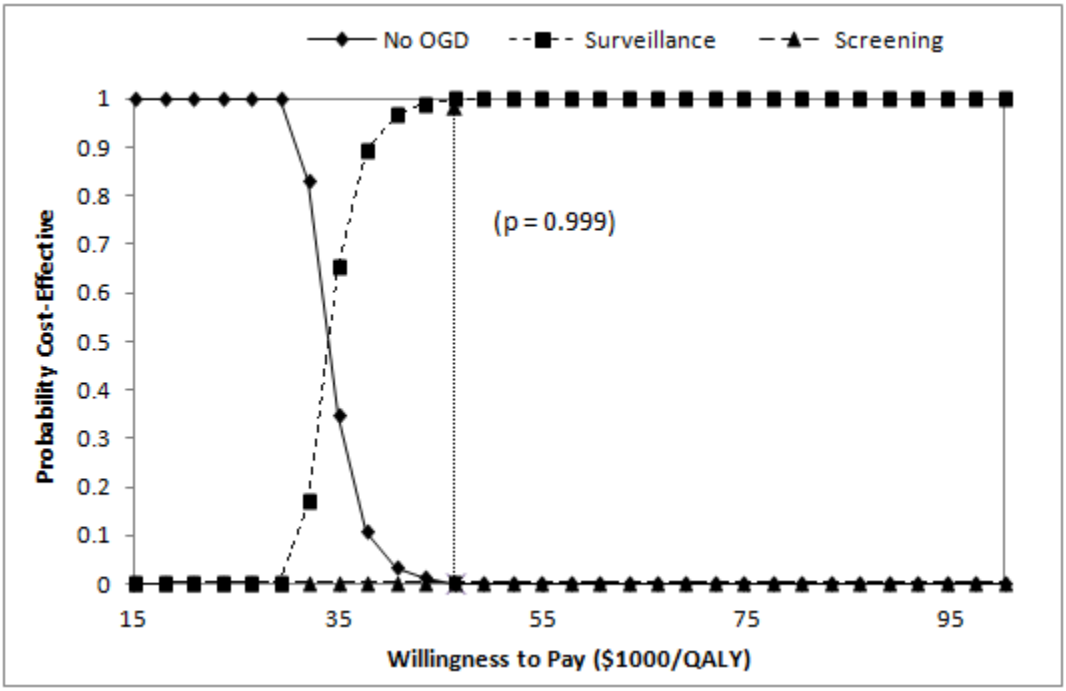


Figure 6-20. Probability of being cost-effective of the three strategies when accounting for uncertainties surrounding the utility of Stage 1 patients

6.4.2 Distributions of gastric cancer stage

Our model will generate two GC patient populations. The first population comprises GC patients diagnosed under usual care with the proportions of Stage 1, Stage 2, Stage 3 and Stage 4 GC cases being 7%, 17%, 33% and 43% respectively. The second population presents the GC patients detected through either the screening or surveillance strategy with stage compositions of 85%:4%:8%:3% for Stage 1:2:3:4. As stated in **5.4.4 Early detection by screening and surveillance**, two Dirichlet distributions, Dir (7:17:33:43) and Dir (85:4:8:3) were used to represent the uncertainties associated with the estimates for proportions of each GC stage for the two patient populations respectively.

Figure 6-21 displays the proportion distribution of Stage 1 GC cases diagnosed under usual care in PSA sampling Dir (7:17:33:43). Figure 6-22 displays the proportion distribution of Stage 1 GC cases detected through follow-up OGD in PSA sampling Dir (85:4:8:3).

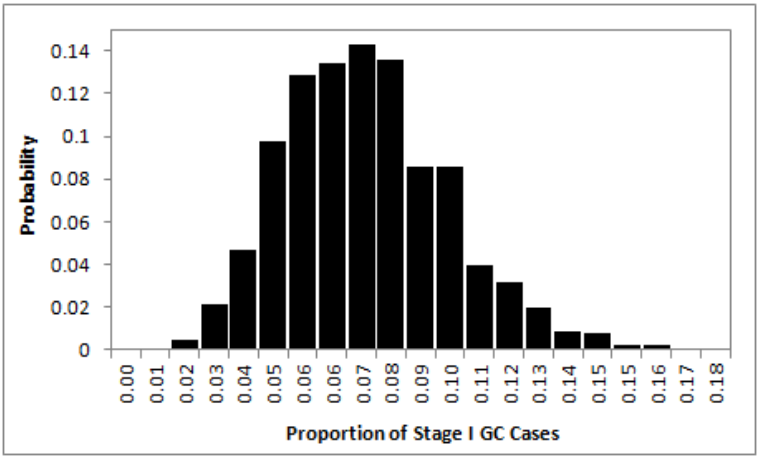


Figure 6-21. Simulated input distribution representing the proportion of Stage 1 cases among gastric cancer patients diagnosed under usual care

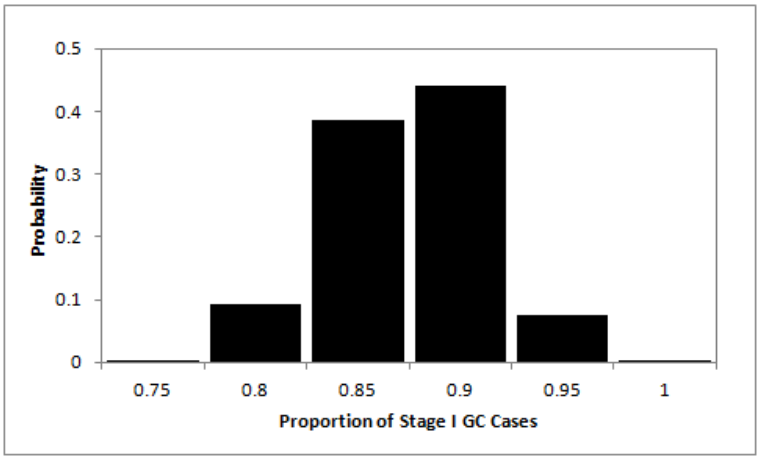


Figure 6-22. Simulated input distribution representing the proportion of Stage 1 cases among the gastric cancer cohort detected by follow-up endoscopy

With the above distributions incorporated, our model projected that surveillance is the cost-effective strategy at the WTP of $ 46,200/QALY (vertical lines in Figure 6-23 and Figure 6-24).

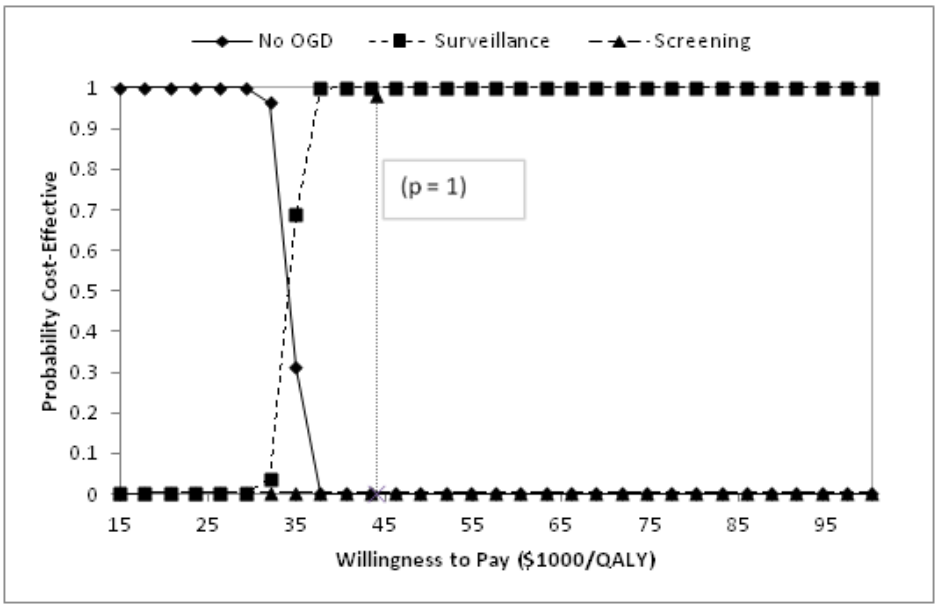


Figure 6-23. Probability of being cost-effective of three strategies when accounting for uncertainties surrounding stage compositions of gastric cancer cohort

.

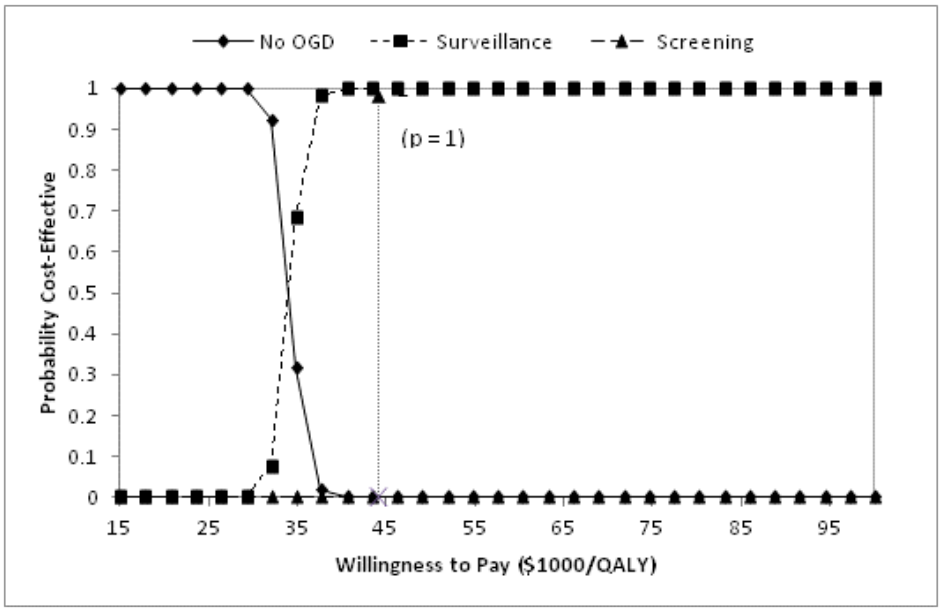


Figure 6-24. Probability of being cost-effective for the three strategies when accounting for uncertainties surrounding the stage composition of gastric cancer cohort

6.4.3 Odds ratio

OR represents the excessive risk for GC associated with high risk projects in the surveillance strategy. It can take only positive values. The log-transformed OR follows a normal distribution. In our model, we fit its uncertainty with a lognormal distribution of N (1.79, 0.90) (Figure 6-25) according to the published data (Watabe et al. 2005).

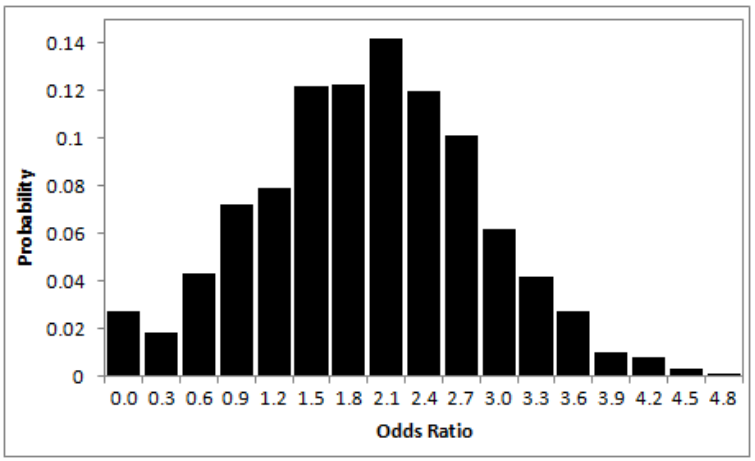


Figure 6-25. Simulated input distribution representing the odds ratio of high risk subjects in the surveillance strategy

In Figure 6-26, it is clear that the precision of OR estimation affects the likelihood of being the cost-effective strategy for all the three strategies. Increasing WTP will give advantage to the surveillance and screening strategies but decreases that probability for no OGD intervention. At the Singapore specific WTP (highlighted with a vertical line), the likelihood that surveillance is cost-effective is 71.2%, higher than that for no OGD intervention (28.8%) and the screening strategy (0%).

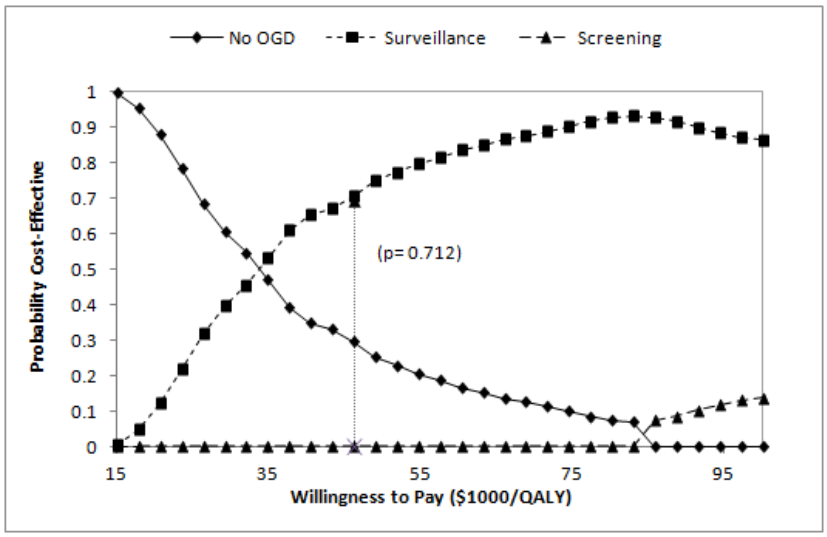


Figure 6-26. Probability of being cost-effective for the three strategies given uncertainties surrounding the odds ratio

6.4.4 Prevalence of precancerous lesions

The prevalence of precancerous lesions indicates the potential GC burden of the target population. Prevalence as a proportion follows binomial distribution. Therefore, the beta distribution (3, 22) was used to fitting the uncertainty around this parameter in the PSA (Figure 6-27).

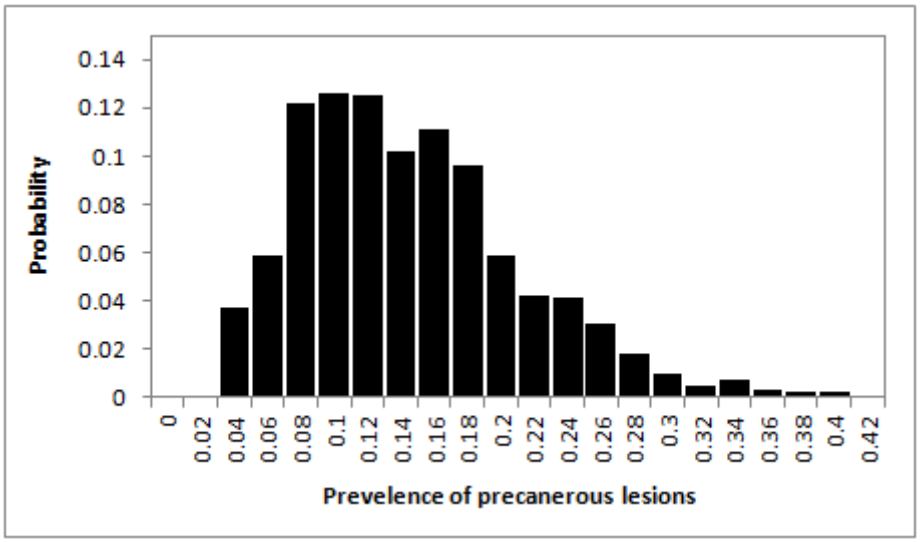


Figure 6-27. Simulated input distribution of prevalence of precancerous lesions

The uncertainty introduced by the current estimate of prevalence of precancerous lesions affects the likelihood of being cost-effective for no OGD intervention and for surveillance. With the increase of WTP, surveillance is more likely to be preferred than no OGD intervention. Given the present model structure for Singapore Chinese, the probability of surveillance being cost-effective is 95.8% (vertical line in Figure 6-28).

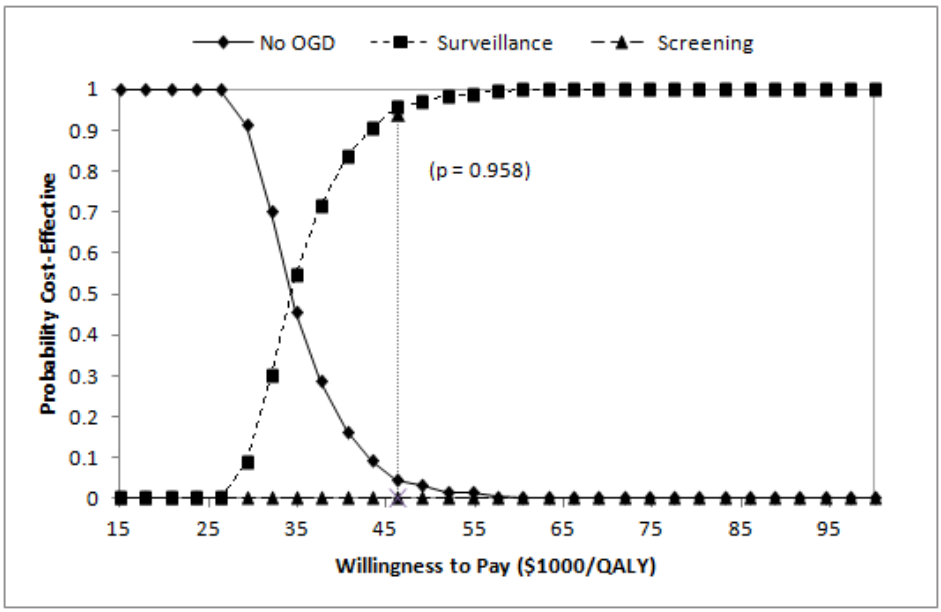


Figure 6-28. Probability of being cost-effective of the three strategies when accounting for uncertainties surrounding prevalence of precancerous lesions.

6.4.5 Age of starting OGD intervention

Unlike the previous eight parameters submitted for PSA to quantify the influence of uncertainty associated with point estimates, age starting OGD follow-up represents the actual age variation among individuals of the target population. This type of variation is referred to as individual variability. To measure its effect on decision making, the original age distribution (Table 6-5) rather than a theoretical distribution was used in the model.

Table 6-5. Population size by age and gender (1000)

Age	Overall	Males	Females
50 - 54	237.7	119.1	118.6
55 - 59	209.0	104.7	104.3
60 - 64	171.1	84.5	86.6
65 - 69	94.8	45.7	49.1

(Department of Statistics Singapore 2012)

In the CEAC by PSA for starting age (Figure 6-29), the probability of the surveillance being the cost-effective strategy is 88.8% for Singapore Chinese. The probability increases if the Singapore healthcare system is willing to pay more for health.

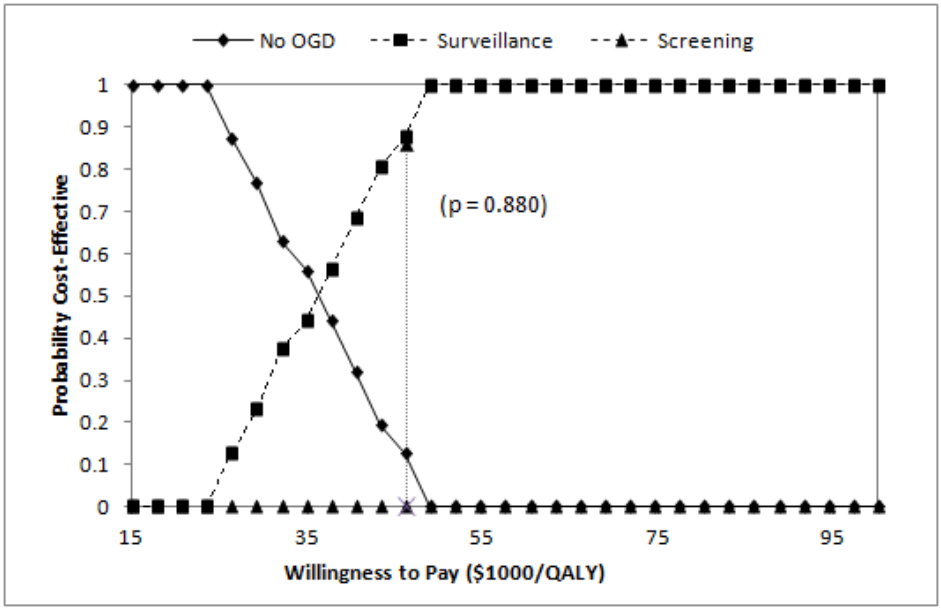


Figure 6-29. Probability of being cost-effective for the three strategies given the age variation among individuals of the target population

In summary, the uncertainties in decision making contributed by individual parameters differ greatly as illustrated by the previous CEACs. Three parameters, OR of high risk subjects for GC, prevalence of precancerous lesions and initial age starting OGD follow-up, exert a stronger effect on the robustness of the choice of optimal strategy. To make an informed decision, we need to understand how these nine parameters and the complex interactions among them jointly contributed to the overall uncertainties in decision-making within the defined Markov structure.

6.4.6 Overall uncertainty in decision making

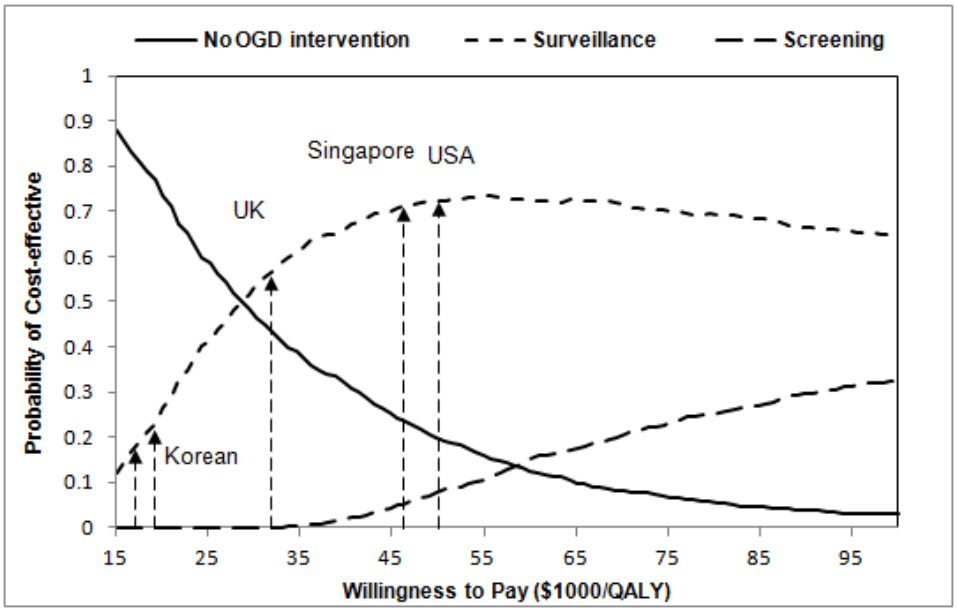


Figure 6-30. Probability of being cost-effective of the three strategies accounting for uncertainties jointly contributed by nine parameters

After accounting for the joint-uncertainties contributed by the stage-specific utilities, the ORs, the prevalence of premalignant lesions and the stage compositions of GC cases, the probability of surveillance being cost-effective is 71.2% at the Singapore WTP threshold of $46,200/QALY (Figure 6-30). Increasing WTP from $15,000/QALY to $54,950/QALY enhances the probability from 12.1% to 73.4%, but no further. Below the WTP threshold of $28,600/QALY, as reported in some Asian studies (Chang et al. 2012; Lee et al. 2007), both screening and surveillance are not cost-effective.

CHAPTER VII: COST-EFFECTIVENESS ANALYSIS -CONCLUSION AND FUTURE WORK

7.1 Overall Assessment of Endoscopic Surveillance for Gastric Cancer

In countries with low to intermediate risk for GC, endoscopic surveillance of precancerous lesions has emerged as an effective and cost-effective strategy for GC prevention. To evaluate the applicability of this strategy to the Singapore healthcare system, we simulated the clinical experience of 50-69 year old Singaporean Chinese at risk of GC. According to our model, focused surveillance using endoscopy is a cost-effective modality compared to population screening. Relative to the usual practice of no OGD intervention, surveillance of the 50-69 year old Chinese population would yield an ICER of $30,033/QALY, which is considered cost-effective against the Singapore-specific WTP of $46,200/QALY and far below the ICER of $421,247/QALY for screening.

The delivery capacity of a healthcare system plays an important role in program implementation. In this regard, surveillance is suggested by our model to be the preferred strategy over screening as the former appears to be less resource intensive and is thus easier for implementation. To avoid similar number of GC deaths in Singapore, our model projected that the number of OGD examinations required is 13.5 and 4.4 for screening and surveillance respectively during a participant's lifetime. Therefore, population-based screening would likely cause a strain on many healthcare systems due to insufficient supply of facilities and qualified endoscopists as it has occurred in some jurisdictions such as Japan (Leung et al. 2008). Additionally, focused surveillance tends to be structured as a hospital-based service, for example the GCEP in Singapore (Zhou et al. 2013), which has shown to be practical and efficient for easy subject recruitment and participation (Chien and Khan 2001). Delivering endoscopic GC surveillance in a hospital-based structure has been proven effective and cost-effective in multiple populations (Dinis-Ribeiro et al. 2007; Whiting et al. 2002).

7.2 Heterogeneity of Endoscopic Surveillance

Given the unique GC risk and all-cause mortality related to age and gender (Department of Statistics Singapore 2012; Singapore Cancer Registry Committee 2012), we explored the heterogeneity of surveillance to inform resource allocation and priority setting among various demographical subgroups. From an economic perspective, resources are prioritized to the areas with lower ICER estimates which imply a better return on investment. Therefore, the 65-69 year old male group with the lowest ICER of $15,285/QALY achieved by surveillance should be favorably considered as a target group for implementing the program. This finding is consistent with a previous model which suggested that the age of 65 years is the optimal age to start OGD follow-up for GC prevention (Dan, So and Yeoh 2006). As male gender and older age are found to be associated with lower ICERs, resources may be allocated to these subpopulations when scaling up a surveillance program.

7.3 Influential Factors for Program Implementation

Through sensitivity analysis, we identified several influential parameters and their relationship with the clinical potential of the surveillance strategy. With this information available to the policy-maker, it is a matter of adjusting and monitoring these parameters to gain the maximum QALYs from a surveillance program. Although varying discount rate and age of starting OGD follow-up can dramatically change the QALY output, the surveillance strategy retains its cost-effectiveness. This demonstrates that the choice of optimal strategy based on our model is quite robust to most influential factors. It has to be noted that, by discounting both cost and effectiveness at the same constant rate, our model underestimated the benefits of surveillance (Bonneux and Birnie 2001). However, being the standard practice in economic evaluation, discounting both allows for meaningful comparisons of ICERs between GC prevention and other public health programs, for example, the existing national screening programs for cervical cancer, colon cancer and breast cancer in Singapore (Yeoh, Chew and Wang 2006).

One central issue for GC surveillance is to define the appropriate precancerous lesions for continuing investigation. Following Correa's model of GC development (Correa 1992), atrophic gastritis, intestinal metaplasia and dysplasia are perceived as premalignant GC lesions and are consequently suggested for OGD follow-up and further investigation (Kapadia 2003). However, the American Society of Gastrointestinal Endoscopy excluded atrophic gastritis (Hirota et al. 2006), and some researchers excluded Type I and Type II intestinal metaplasia as indications for OGD follow-up (Rugge et al. 2003). Our model employed OR to distinguish high risk groups from the general population. The sensitivity analysis suggested that the premalignant lesions associated with an OR of 3.11 or above would produce favorable cost-effectiveness ratios for surveillance strategy. Considering epidemiologic evidence showing that the risk of GC associated with atrophic gastritis, intestinal metaplasia and dysplasia are all higher than 3.11 (Uemura et al. 2001; Vannella et al. 2010; Watabe et al. 2005), our findings support the practice of monitoring most clinically suspected premalignant GC lesions. Moreover, it is implied that OGD surveillance could be extended to other subpopulations, such as those with a positive family history (Huang and Hunt 2003).

In our study, the program cost proportion of total operating cost not only represents the magnitude of expenditure on supporting activities in the delivery of endoscopic surveillance, but also highlights the competition for resources between supporting activities and essential medical services of OGD examination (Subramanian et al. 2011). Our model examined this proportion as a parameter indicating operational efficiency of an actual program. According to the sensitivity analysis, the proportion of program cost cannot exceed 67% of total operation budget. Otherwise, a surveillance program would be considered inefficient in its operation and generate ICERs above the Singapore WTP. As such, the program cost proportion of 67% can be set as the standard to assess the actual performance of an OGD surveillance program in Singapore, such as the GCEP (Zhou et al. 2013). A similar approach may be adopted when evaluating the efficiency of similar programs in other jurisdictions.

Utility of stage 1 GC patients was found to be an influential parameter in our model. This provides evidence of the credibility of our model as this finding reflects one of the principles of secondary prevention, i.e., better clinical outcomes can be achieved when clinical interventions are administered at earlier stages (Leon Gordis 2009). The EQ-5D score of 0.63 was identified as the minimum utility of early stage GC patients for a cost-effective surveillance program in Singapore. For Stage 1 GC patients, a EQ-5D score of 0.88 has been reported previously by our research group (Zhou et al. 2012). A better quality of life for patients could be anticipated if a surveillance program was fully functional. Evidence have shown that GC patients detected by prevention programs are more likely to receive endoscopic procedures which would result in better outcomes than conventional surgery-based regimens (Ang,Khor and Gotoda 2010; Nam et al. 2009). Assigning the same utility to GC patients for the three strategies compared in our model, we intentionally based our choice of the surveillance strategy on conservative cost-effective ratios.

The cost of OGD in our study has a great impact on cost-effectiveness estimation as in the model by Dan et al (Dan, So and Yeoh 2006). According to our model, endoscopic surveillance would become too expensive for Singapore healthcare system when the OGD cost raises above $624. Considering that the OGD cost in Singapore is one of the most expensive in Asia, OGD-based surveillance may not appear attractive to policy-makers. However, this parameter is the modifiable factor suggesting that OGD cost can be determined by health policy and healthcare market. In our model for example, OGD examination is cost at $340 which was the result of negotiation between the GCEP and the National University Hospital. It is cheaper than the normal hospital rate (Zhou et al. 2013).

7.4 Robustness of the Findings

Endoscopic surveillance appears to be the cost-effective given the ICERs estimated in our model. However, a decision solely based on a fixed ICER is premature considering the inherent imperfection with the estimates for input parameters. The PSA in our study has quantified the extent to which

uncertainties of the nine parameters have influenced our decision. As shown in the cost-effectiveness acceptability curve Figure 6-30, we are 71.2% confident that surveillance is the optimal strategy for GC prevention in Singapore. The likelihood favoring screening or no OGD intervention is 5.1% and 23.7% respectively. The acceptability curve also showed that, based on the reported WTP thresholds, OGD surveillance may not be a better choice than currently no OGD intervention in developing countries of Asia. As confirmed in a Taiwanese population, an *H. pylori* eradication strategy was preferred over endoscopic surveillance (Lee et al. 2007).

7.5 Strength and Limitation

A few strengths about this project are noted. The most significant characteristic is that we investigated both utility and cost of the target population for this model. Allowing for future implementation, we represented program cost as a proportion of operating cost in order to inform program operation. For the surveillance strategy, we employed the OR rather than the progression rate to categorize the target population on the basis of GC risk, thereby providing evidence to identify appropriate people for OGD follow-up.

Nevertheless, the study does have some limitations. To mitigate the lead-time bias and length-time bias toward screening or surveillance, GC patients were assumed to have the same survival experience whether they have been detected favorably by prevention programs. We also adjusted the structure of the Markov trees to ensure consistent GC incidences across three strategies. As a result, extra survival caused by length-time and lead-time bias was alleviated for screening or surveillance. However we cannot completely rule out their existence. Furthermore, we assumed a 100% compliance rate with the OGD schedule, which is unlikely in reality (Choi et al. 2009; Kwon et al. 2009). However, in the present situation, this study aims to provide a conceptual assessment of the cost-effectiveness potential of a surveillance strategy for future program implementation. To this end, our model has provided useful data to avoid conceptual deficit (Shapiro 1982).

7.6 Conclusion

In conclusion, endoscopic surveillance of premalignant gastric lesions is potentially a cost-effective strategy for GC control for populations with low to intermediate risk, such as the Singaporean Chinese. To realize this potential, correct identification of high-risk subjects, efficient program operation and the utility of early GC cases are important concerns for program implementation. Policy-makers also need to consider the issues specific to their healthcare systems, such as the cost of providing the OGD service, discount rate and WTP threshold adopted by the society. Despite several concerns, potentially endoscopic surveillance is still the optimal strategy for these populations.

7.7 Future Work

As seen in the process of model construction (**CHAPTER V: COST EFFECTIVENESS ANALYSIS - MARKOV MODEL CONSTRUCTION**), the model validity is largely constrained by the availability of data. To improve the validity and usefulness of our model, the following studies would be greatly beneficial.

7.7.1 Cost of illness of gastric cancer

A well-designed cost of illness study investigating lifetime cost of a GC patient is necessary. Cancer disease is a lifetime disease. Once diagnosed, a life-long medical care is required, strictly meaning a life-long medical cost until the death. This imposes a tremendous economic burden on individual cancer patients and the society. Besides medical factors, many non-medical factors also increase this economic burden even when they do not necessarily affect the disease progression, such as inflation or lack of family care. A cost of illness analysis is able to measure the resources consumed in initial, maintenance and terminal stage of a GC patient. The analysis will not only quantify the expected cost of an average GC patient, but also identify medical and non-medical factors affecting cost generation.

With such a study in place, the current model would greatly improve the reliability and precision of model outputs. The findings can be interpreted in a quantitative manner.

7.7.2 In-hospital mortality of a gastric cancer patient

In-hospital mortality stands by itself an informative parameter of quality of care. It is theoretically intuitive that in-hospital mortality, which could be a result of various factors relevant to surgery, peri- and post-operative care, and basic medical care, can affect the costs and quality of life immediately and for a long time. As of completion of the present study, in-hospital mortality data have not been reported in Singapore. A study estimating in-hospital morality and predictive factors will improve our model dramatically.

7.7.3 Prevalence of precancerous lesions

As the fundamental epidemiologic basis for GC surveillance, prevalence of precancerous lesions should be derived from a population-based survey. However, such a study is not available for Singapore Chinese population. Our model was obliged to use an estimate jointly determined by GCEP (Zhu et al. 2009), a small community survey (Ang et al. 2005) and model calibration. A cross-sectional survey should be conducted to investigate histologic prevalence of gastric premalignancies in the target population and different subgroups. When it comes to program implementation, this information will be very useful for resources allocation and priority setting.

7.7.4 A model based on a dynamic cohort

The current cohort-based model simulates a static cohort neglecting the fact that the target population is evolving constantly. Naturally a model based on a dynamic population is more appropriate and meaningful, which allows for the population changes due to economic and social reasons. The value of current model is somewhat undermined by the possibility that the model may miss out important

factors capable of affecting cost-effectiveness of the evaluated strategies. A discrete event model simulating a dynamic population is in the planning phase.

7.7.5 An empirical model based on GCEP

The follow-up of GCEP subjects is still ongoing. GCEP is a comprehensive project which is supposed to capture the information about GC incidence and mortality, progression rates of major precancerous lesions and all-cause mortality for high risk subjects. The data from such a real prospective cohort is ideal for an empirical model.

The current model attempted to be an empirical model in the beginning. At the time of model construction, however, the GCEP follow-up is not sufficiently long to produce reliable data. Once the GCEP is completed, the current model will incorporate the updated information and evolve into a more empirical model, from which the findings are more convincing.

REFERENCES

Aarnio, M., R. Salovaara, L. A. Aaltonen, J. P. Mecklin and H. J. Jarvinen (1997). "Features of gastric cancer in hereditary non-polyposis colorectal cancer syndrome." Int J Cancer 74(5): 551-555.

Amedei, A., M. Benagiano, C. della Bella, E. Niccolai and M. M. D'Elios (2011). "Novel immunotherapeutic strategies of gastric cancer treatment." J Biomed Biotechnol 2011: 437348.

Ang, T. L., K. M. Fock, S. Dhamodaran, E. K. Teo and J. Tan (2005). "Racial differences in Helicobacter pylori, serum pepsinogen and gastric cancer incidence in an urban Asian population." J Gastroenterol Hepatol 20(10): 1603-1609.

Ang, T. L., C. J. Khor and T. Gotoda (2010). "Diagnosis and endoscopic resection of early gastric cancer." Singapore Med J 51(2): 93-100.

Anikeeva, O., P. Bi, J. E. Hiller, P. Ryan, D. Roder and G. S. Han (2012). "Trends in cancer mortality rates among migrants in Australia: 1981-2007." Cancer Epidemiol 36(2): e74-82.

Babazono, A. and A. L. Hillman (1995). "Declining cost-effectiveness of screening for disease. The case of gastric cancer in Japan." Int J Technol Assess Health Care 11(2): 354-364.

Barbosa, C., B. Taylor, C. Godfrey, J. Rehm, S. Parrott and C. Drummond (2010). "Modelling lifetime QALYs and health care costs from different drinking patterns over time: a Markov model." Int J Methods Psychiatr Res 19(2): 97-109.

Baron, R. C., B. K. Rimer, R. J. Coates, J. Kerner, G. P. Kalra, S. Melillo, N. Habarta, K. M. Wilson, S. Chattopadhyay and K. Leeks (2008). "Client-directed interventions to increase community access to breast, cervical, and colorectal cancer screening a systematic review." Am J Prev Med 35(1 Suppl): S56-66.

Bautista-Arredondo, S., P. Gadsden, J. E. Harris and S. M. Bertozzi (2008). "Optimizing resource allocation for HIV/AIDS prevention programmes: an analytical framework." AIDS 22 Suppl 1: S67-74.

Bertuccio, P., L. Chatenoud, F. Levi, D. Praud, J. Ferlay, E. Negri, M. Malvezzi and C. La Vecchia (2009). "Recent patterns in gastric cancer: a global overview." Int J Cancer 125(3): 666-673.

Blaser, M. J. (1999). "Hypothesis: the changing relationships of Helicobacter pylori and humans: implications for health and disease." J Infect Dis 179(6): 1523-1530.

Bonneux, L. and E. Birnie (2001). "The discount rate in the economic evaluation of prevention: a thought experiment." J Epidemiol Community Health 55(2): 123-125.

Breen, N. and M. L. Brown (1994). "The price of mammography in the United States: data from the National Survey of Mammography Facilities." The Milbank quarterly 72(3): 431-450.

Bustamante, M., F. Devesa, A. Borghol, J. Ortuno and M. J. Ferrando (2002). "Accuracy of the initial endoscopic diagnosis in the discrimination of gastric ulcers: is endoscopic follow-up study always needed?" J Clin Gastroenterol 35(1): 25-28.

Cardoso, R., N. G. Coburn, R. Seevaratnam, A. Mahar, L. Helyer, C. Law and S. Singh (2012). "A systematic review of patient surveillance after curative gastrectomy for gastric cancer: a brief review." Gastric Cancer 15 Suppl 1: S164-167.

Cella, D. (1997). FACIT Manual: Manual of the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. Evanston, CORE.

Centers for Disease Control and Prevention, N. B. C. C. E. D. P. (2005). Policies and Procedures manual. Atlanta, Centers Disease Control & Prevention, .

Chang, H. S., E. C. Park, W. Chung, C. M. Nam, K. S. Choi, E. Cho and W. H. Cho (2012). "Comparing endoscopy and upper gastrointestinal X-ray for gastric cancer screening in South Korea: a cost-utility analysis." Asian Pac J Cancer Prev 13(6): 2721-2728.

Cheung, Y. B., R. Daniel and G. Y. Ng (2006). "Response and non-response to a quality-of-life question on sexual life: a case study of the simple mean imputation method." Qual Life Res 15(9): 1493-1501.

Cheung, Y. B., C. Goh, J. Thumboo, K. S. Khoo and J. Wee (2005). "Variability and sample size requirements of quality-of-life measures: a randomized study of three major questionnaires." J Clin Oncol 23(22): 4936-4944.

Cheung, Y. B., C. Goh, J. Wee, K. S. Khoo and J. Thumboo (2009). "Measurement properties of the Chinese language version of the functional assessment of cancer therapy-general in a Singaporean population." Ann Acad Med Singapore 38(3): 225-229.

Cheung, Y. B., J. Thumboo, C. Goh, K. S. Khoo, W. Che and J. Wee (2004). "The equivalence and difference between the English and Chinese versions of two major, cancer-specific, health-related quality-of-life questionnaires." Cancer 101(12): 2874-2880.

Cheung, Y. B., L. C. Wong, M. H. Tay, C. K. Toh, W. H. Koo, R. Epstein and C. Goh (2004). "Order effects in the assessment of quality of life in cancer patients." Qual Life Res 13(7): 1217-1223.

Chien, P. F. and K. S. Khan (2001). "Evaluation of a clinical test. II: Assessment of validity." BJOG 108(6): 568-572.

Cho, A., A. Chaudhry, L. Minsky-Primus, A. Tso, G. Perez-Perez, D. Diehl, S. G. Marcus and F. M. Gany (2006). "Acceptance of repeat esophagogastroduodenoscopy to detect gastric cancer in a Chinese immigrant cohort." J Clin Gastroenterol 40(7): 606-611.

Cho, E., M. H. Kang, K. S. Choi, M. Suh, J. K. Jun and E. C. Park (2013). "Cost-effectiveness outcomes of the national gastric cancer screening program in South Korea." Asian Pac J Cancer Prev 14(4): 2533-2540.

Choi, K. S., M. S. Kwak, H. Y. Lee, J. K. Jun, M. I. Hahm and E. C. Park (2009). "Screening for gastric cancer in Korea: population-based preferences for endoscopy versus upper gastrointestinal series." Cancer Epidemiol Biomarkers Prev 18(5): 1390-1398.

Commission on Macroeconomics and Health (2001). Macroeconomics and Health: Investing in Health for Economic Development. Geneva, World Health Organization.

Conroy, T., L. Uwer and M. Deblock (2007). "Health-related quality-of-life assessment in gastrointestinal cancer: are results relevant for clinical practice?" Curr Opin Oncol 19(4): 401-406.

Correa, P. (1992). "Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention." Cancer Res 52(24): 6735-6740.

Correa, P., E. T. Fontham, J. C. Bravo, L. E. Bravo, B. Ruiz, G. Zarama, J. L. Realpe, G. T. Malcom, D. Li, W. D. Johnson and R. Mera (2000). "Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy." J Natl Cancer Inst 92(23): 1881-1888.

Correa, P., M. B. Piazuelo and M. C. Camargo (2004). "The future of gastric cancer prevention." Gastric Cancer 7(1): 9-16.

D.Ellis, P. (2010). The Essential Guide to Effect Sizes: An Introduction to Statistical Power, Meta-Analysis and the Interpretation of Research Results. . Cambridge, Cambridge University Press.

Dan, Y. Y., J. B. So and K. G. Yeoh (2006). "Endoscopic screening for gastric cancer." Clin Gastroenterol Hepatol 4(6): 709-716.

Davis, P., M. Hakama, S. Hisamichi, T. Kakizoe, T. Sano and T. Sugimura (2000). "Report of the Thirteenth International Symposium of the Foundation for Promotion of Cancer Research: cancer screening-past, present and future." Jpn J Clin Oncol 30(7): 322-331.

de Vries, A. C., J. Haringsma and E. J. Kuipers (2007). "The detection, surveillance and treatment of premalignant gastric lesions related to Helicobacter pylori infection." Helicobacter 12(1): 1-15.

Debb, S. M., B. Arnold, B. Perez and D. Cella (2011). "Validation of the FACT-Gastric cancer quality of life questionnaire for use in Spanish-speaking countries." Psychooncology 20(1): 19-27.

Denis, B., M. Ruetsch, P. Strentz, J. Y. Vogel, F. Guth, J. M. Boyaval, X. Pagnon, J. F. Ebelin, I. Gendre and P. Perrin (2007). "Short term outcomes of the first round of a pilot colorectal cancer screening programme with guaiac based faecal occult blood test." Gut 56: 1579-1584.

Department of Statistics Singapore (2012). Yearbook of Statistics Singapore 2012. Singapore Ministry of Trade & Industry, Republic of Singapore.

Desgagne, A., A. M. Castilloux, J. F. Angers and J. LeLorier (1998). "The use of the bootstrap statistical method for the pharmacoeconomic cost analysis of skewed data." Pharmacoeconomics 13: 487-497.

Di Giulio, E., C. Hassan, P. J. Pickhardt, A. Zullo, A. Laghi, D. H. Kim and F. Iafrate (2009). "Cost-effectiveness of upper gastrointestinal endoscopy according to the appropriateness of the indication." Scand J Gastroenterol 44(4): 491-498.

Dinis-Ribeiro, M., A. da Costa-Pereira, C. Lopes and L. Moreira-Dias (2007). "Feasibility and cost-effectiveness of using magnification chromoendoscopy and pepsinogen serum levels for the follow-up of patients with atrophic chronic gastritis and intestinal metaplasia." J Gastroenterol Hepatol 22(10): 1594-1604.

Dolan, P. and C. Gudex (1995). "Time preference, duration and health state valuations." Health Econ 4(4): 289-299.

Drummond, M. F., Sculpher, Mark J., Torrance, George W., O'Brien, Bernie J. and Stoddart, Greg L. (2005). Methods for the Economic Evaluation of Health Care Programmes. Oxford, Oxford University Press.

Eddy, D. M., W. Hollingworth, J. J. Caro, J. Tsevat, K. M. McDonald and J. B. Wong (2012). "Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--7." Value Health 15(6): 843-850.

Ekwueme, D. U., J. G. Gardner, S. Subramanian, F. K. Tangka, B. Bapat and L. C. Richardson (2008). "Cost analysis of the National Breast and Cervical Cancer Early Detection Program: selected states, 2003 to 2004." Cancer 112(3): 626-635.

Ekwueme, D. U., I. J. Hall, L. C. Richardson, J. G. Gardner, J. Royalty and T. D. Thompson (2008). "Estimating personal costs incurred by a woman participating in mammography screening in the National Breast and Cervical Cancer Early Detection Program." Cancer 113(3): 592-601.

El-Zimaity, H. M., J. Ramchatesingh, M. A. Saeed and D. Y. Graham (2001). "Gastric intestinal metaplasia: subtypes and natural history." J Clin Pathol 54(9): 679-683.

Environmental Protection Agency USA (2000). Cost of Stomach Cancer. Cost of Illness Handbook. washington DC, Environmental Protection Agency USA: 1-45.

Fairclough, D. L. and D. F. Cella (1996). "Functional Assessment of Cancer Therapy (FACT-G): non-response to individual questions." Qual Life Res 5(3): 321-329.

Fendrick, A. M., M. E. Chernew, R. A. Hirth, B. S. Bloom, R. R. Bandekar and J. M. Scheiman (1999). "Clinical and economic effects of population-based Helicobacter pylori screening to prevent gastric cancer." Arch Intern Med 159(2): 142-148.

Ferlay J, B. F., Pisani P, Parkin DM., (2004). GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide. . Lyon, France, IARC Pess.

Figueiredo, C., J. C. Machado, P. Pharoah, R. Seruca, S. Sousa, R. Carvalho, A. F. Capelinha, W. Quint, C. Caldas, L. J. van Doorn, F. Carneiro and M. Sobrinho-Simoes (2002). "Helicobacter pylori and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma." J Natl Cancer Inst 94(22): 1680-1687.

Filomena, A., C. Saieva, V. Lucchetti, F. Santacroce, P. Falorni, V. Francini, P. Carrieri, E. Zini, B. Ridolfi, P. Belli, B. Orsini, P. Mandi, D. Palli and S. Scheggi (2011). "Gastric cancer surveillance in a high-risk population in tuscany (Central Italy): preliminary results." Digestion 84(1): 70-77.

Fock, K. M. and T. L. Ang (2010). "Epidemiology of Helicobacter pylori infection and gastric cancer in Asia." J Gastroenterol Hepatol 25(3): 479-486.

Fock, K. M., P. Katelaris, K. Sugano, T. L. Ang, R. Hunt, N. J. Talley, S. K. Lam, S. D. Xiao, H. J. Tan, C. Y. Wu, H. C. Jung, B. H. Hoang, U. Kachintorn, K. L. Goh, T. Chiba and A. A. Rani (2009). "Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection." J Gastroenterol Hepatol 24(10): 1587-1600.

Fock, K. M., N. Talley, P. Moayyedi, R. Hunt, T. Azuma, K. Sugano, S. D. Xiao, S. K. Lam, K. L. Goh, T. Chiba, N. Uemura, J. G. Kim, N. Kim, T. L. Ang, V. Mahachai, H. Mitchell, A. A. Rani, J. M. Liou, R. K. Vilaichone and J. Sollano (2008). "Asia-Pacific consensus guidelines on gastric cancer prevention." J Gastroenterol Hepatol 23(3): 351-365.

Ford, A. C. and P. Moayyedi (2009). "Redundant data in the meta-analysis on Helicobacter pylori eradication." Ann Intern Med 151(7): 513; author reply 513-514.

Forman, D. and V. J. Burley (2006). "Gastric cancer: global pattern of the disease and an overview of environmental risk factors." Best Pract Res Clin Gastroenterol 20(4): 633-649.

Frew, E., J. L. Wolstenholme, W. Atkin and D. K. Whynes (1999). "Estimating time and travel costs incurred in clinic based screening: flexible sigmoidoscopy screening for colorectal cancer." Journal of medical screening 6(3): 119-123.

Fumimoto, H., K. Kobayashi, C. H. Chang, S. Eremenco, Y. Fujiki, S. Uemura, Y. Ohashi and S. Kudoh (2001). "Cross-cultural validation of an international questionnaire, the General Measure of the Functional Assessment of Cancer Therapy scale (FACT-G), for Japanese." Qual Life Res 10(8): 701-709.

Gao, F., G. Y. Ng, Y. B. Cheung, J. Thumboo, G. Pang, W. H. Koo, V. K. Sethi, J. Wee and C. Goh (2009). "The Singaporean English and Chinese versions of the EQ-5D achieved measurement equivalence in cancer patients." J Clin Epidemiol 62(2): 206-213.

Garland, S. N., G. Pelletier, A. Lawe, B. J. Biagioni, J. Easaw, M. Eliasziw, D. Cella and O. F. Bathe (2011). "Prospective evaluation of the reliability, validity, and minimally important difference of the functional assessment of cancer therapy-gastric (FACT-Ga) quality-of-life instrument." Cancer 117(6): 1302-1312.

Gonzalez, C. A., G. Pera, A. Agudo, D. Palli, V. Krogh, P. Vineis, R. Tumino, S. Panico, G. Berglund, H. Siman, O. Nyren, A. Agren, C. Martinez, M. Dorronsoro, A. Barricarte, M. J. Tormo, J. R. Quiros, N. Allen, S. Bingham, N. Day, A. Miller, G. Nagel, H. Boeing, K. Overvad, A. Tjonneland, H. B. Bueno-De-Mesquita, H. C. Boshuizen, P. Peeters, M. Numans, F. Clavel-Chapelon, I. Helen, E. Agapitos, E. Lund, M. Fahey, R. Saracci, R. Kaaks and E. Riboli (2003). "Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC)." Int J Cancer 107(4): 629-634.

Graham, D. Y. and M. Asaka (2010). "Eradication of gastric cancer and more efficient gastric cancer surveillance in Japan: two peas in a pod." Journal of gastroenterology 45(1): 1-8.

Grazzini, G., S. Ciatto, C. Cislaghi, G. Castiglione, M. Falcone, P. Mantellini and M. Zappa (2008). "Cost evaluation in a colorectal cancer screening programme by faecal occult blood test in the District of Florence." J Med Screen 15: 175-181.

Guadagni, S., M. Catarci, T. Kinoshita, M. Valenti, G. De Bernardinis and M. Carboni (1997). "Causes of death and recurrence after surgery for early gastric cancer." World J Surg 21(4): 434-439.

Guggenheim, D. E. and M. A. Shah (2013). "Gastric cancer epidemiology and risk factors." J Surg Oncol 107(3): 230-236.

Hamashima, C., T. Sobue, Y. Muramatsu, H. Saito, N. Moriyama and T. Kakizoe (2006). "Comparison of observed and expected numbers of detected cancers in the research center for cancer prevention and screening program." Jpn J Clin Oncol 36(5): 301-308.

Han, J. Y., H. Son, W. C. Lee and B. G. Choi (2003). "The correlation between gastric cancer screening method and the clinicopathologic features of gastric cancer." Med Oncol 20(3): 265-269.

Hassan, C., A. Zullo, E. Di Giulio, B. Annibale, E. Lahner, V. De Francesco and E. Ierardi (2010). "Cost-effectiveness of endoscopic surveillance for gastric intestinal metaplasia." Helicobacter 15(3): 221-226.

Heitman, S. J., F. Au, B. J. Manns, S. E. McGregor and R. J. Hilsden (2008). "Nonmedical costs of colorectal cancer screening with the fecal occult blood test and colonoscopy." Clin Gastroenterol Hepatol 6(8): 912-917 e911.

Helicobacter pylori and Cancer Collaborative Group (2001). "Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts." Gut 49(3): 347-353.

Hirota, W. K., M. J. Zuckerman, D. G. Adler, R. E. Davila, J. Egan, J. A. Leighton, W. A. Qureshi, E. Rajan, R. Fanelli, J. Wheeler-Harbaugh, T. H. Baron and D. O. Faigel (2006). "ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract." Gastrointest Endosc 63(4): 570-580.

Hisamichi, S. (1989). "Screening for gastric cancer." World J Surg 13(1): 31-37.

Holzner, B., G. Kemmler, B. Sperner-Unterweger, M. Kopp, M. Dunser, R. Margreiter, I. Marschitz, D. Nachbaur, W. W. Fleischhacker and R. Greil (2001). "Quality of life measurement in oncology--a matter of the assessment instrument?" Eur J Cancer 37(18): 2349-2356.

Hosokawa, O., T. Miyanaga, Y. Kaizaki, M. Hattori, K. Dohden, K. Ohta, Y. Itou and H. Aoyagi (2008). "Decreased death from gastric cancer by endoscopic screening: association with a population-based cancer registry." Scand J Gastroenterol 43(9): 1112-1115.

Huang, C. C., H. H. Lien, P. C. Wang, J. C. Yang, C. Y. Cheng and C. S. Huang (2007). "Quality of life in disease-free gastric adenocarcinoma survivors: impacts of clinical stages and reconstructive surgical procedures." Dig Surg 24(1): 59-65.

Huang, J. Q. and R. H. Hunt (2003). "The evolving epidemiology of Helicobacter pylori infection and gastric cancer." Can J Gastroenterol 17 Suppl B: 18B-20B.

Isobe, Y., A. Nashimoto, K. Akazawa, I. Oda, K. Hayashi, I. Miyashiro, H. Katai, S. Tsujitani, Y. Kodera, Y. Seto and M. Kaminishi (2011). "Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry." Gastric Cancer 14(4): 301-316.

Jacobs, P. and J. F. Baladi (1996). "Biases in cost measurement for economic evaluation studies in health care." Health economics 5(6): 525-529.

Jemal, A., F. Bray, M. M. Center, J. Ferlay, E. Ward and D. Forman (2011). "Global cancer statistics." CA Cancer J Clin 61(2): 69-90.

Johns, B., R. Baltussen and R. Hutubessy (2003). "Programme costs in the economic evaluation of health interventions." Cost Eff Resour Alloc 1: 1.

Joossens, J. V., M. J. Hill, P. Elliott, R. Stamler, E. Lesaffre, A. Dyer, R. Nichols and H. Kesteloot (1996). "Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group." Int J Epidemiol 25(3): 494-504.

Kamineni, A., M. A. Williams, S. M. Schwartz, L. S. Cook and N. S. Weiss (1999). "The incidence of gastric carcinoma in Asian migrants to the United States and their descendants." Cancer Causes Control 10(1): 77-83.

Kapadia, C. R. (2003). "Gastric atrophy, metaplasia, and dysplasia: a clinical perspective." J Clin Gastroenterol 36(5 Suppl): S29-36; discussion S61-22.

Kim, Y., J. K. Jun, K. S. Choi, H. Y. Lee and E. C. Park (2011). "Overview of the National Cancer screening programme and the cancer screening status in Korea." Asian Pac J Cancer Prev 12(3): 725-730.

Kim, Y. S., H. A. Park, B. S. Kim, J. H. Yook and M. S. Lee (2000). "Efficacy of screening for gastric cancer in a Korean adult population: a case-control study." J Korean Med Sci 15(5): 510-515.

Knudsen, A. B., P. M. McMahon and G. S. Gazelle (2007). "Use of modeling to evaluate the cost-effectiveness of cancer screening programs." j Clin Oncol 25(2): 203-208.

Kong, S. H., D. J. Park, H. J. Lee, H. C. Jung, K. U. Lee, K. J. Choe and H. K. Yang (2004). "Clinicopathologic features of asymptomatic gastric adenocarcinoma patients in Korea." Jpn J Clin Oncol 34(1): 1-7.

Koong, H. N., H. S. Chan, R. Nambiar, K. C. Soo, J. Ho, H. S. Ng and E. H. Ng (1996). "Gastric cancers in Singapore: poor prognosis arising from late presentation." Aust N Z J Surg 66(12): 813-815.

Kubota, H., T. Kotoh, R. Masunaga, D. K. Dhar, M. Shibakita, M. Tachibana, H. Kohno and N. Nagasue (2000). "Impact of screening survey of gastric cancer on clinicopathological features and survival: retrospective study at a single institution." Surgery 128(1): 41-47.

Kwon, D. H., M. P. Dore, J. J. Kim, M. Kato, M. Lee, J. Y. Wu and D. Y. Graham (2003). "High-level beta-lactam resistance associated with acquired multidrug resistance in Helicobacter pylori." Antimicrob Agents Chemother 47(7): 2169-2178.

Kwon, Y. M., H. T. Lim, K. Lee, B. L. Cho, M. S. Park, K. Y. Son and S. M. Park (2009). "Factors associated with use of gastric cancer screening services in Korea." World J Gastroenterol 15(29): 3653-3659.

Kye, S. Y., E. O. Han and K. H. Park (2010). "Predictors of regular gastric cancer screening among Koreans." Asian Pac J Cancer Prev 11(5): 1315-1320.

Ladeiras-Lopes, R., A. K. Pereira, A. Nogueira, T. Pinheiro-Torres, I. Pinto, R. Santos-Pereira and N. Lunet (2008). "Smoking and gastric cancer: systematic review and meta-analysis of cohort studies." Cancer Causes Control 19(7): 689-701.

Langenhoff, B. S., P. F. Krabbe, T. Wobbes and T. J. Ruers (2001). "Quality of life as an outcome measure in surgical oncology." Br J Surg 88(5): 643-652.

Larsson, S. C., L. Bergkvist and A. Wolk (2006). "Fruit and vegetable consumption and incidence of gastric cancer: a prospective study." Cancer Epidemiol Biomarkers Prev 15(10): 1998-2001.

Lauren, P. (1965). "The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. An Attempt at a Histo-Clinical Classification." Acta Pathol Microbiol Scand 64: 31-49.

Lawrence, W., Jr. (2008). "On quality of life in the long-term survivors after total gastrectomy for gastric carcinoma." J Surg Oncol 97(2): 131.

Lee, K. J., M. Inoue, T. Otani, M. Iwasaki, S. Sasazuki and S. Tsugane (2006). "Gastric cancer screening and subsequent risk of gastric cancer: a large-scale population-based cohort study, with a 13-year follow-up in Japan." Int J Cancer 118(9): 2315-2321.

Lee, Y. C., J. T. Lin, H. M. Wu, T. Y. Liu, M. F. Yen, H. M. Chiu, H. P. Wang, M. S. Wu and T. Hsiu-Hsi Chen (2007). "Cost-effectiveness analysis between primary and secondary preventive strategies for gastric cancer." Cancer Epidemiol Biomarkers Prev 16: 875-885.

Legood, R., A. M. Gray, C. Mahe, J. Wolstenholme, K. Jayant, B. M. Nene, S. S. Shastri, S. G. Malvi, R. Muwonge, A. M. Budukh and R. Sankaranarayanan (2005). "Screening for cervical cancer in India: How much will it cost? A trial based analysis of the cost per case detected." Int J Cancer 117(6): 981-987.

Lello, E., B. Furnes and T. H. Edna (2007). "Short and long-term survival from gastric cancer. A population-based study from a county hospital during 25 years." Acta Oncol 46(3): 308-315.

Leon Gordis (2009). Epidemiology. Philadelphia, Saunders Elsevier.

Leung, W. K., M. S. Wu, Y. Kakugawa, J. J. Kim, K. G. Yeoh, K. L. Goh, K. C. Wu, D. C. Wu, J. Sollano, U. Kachintorn, T. Gotoda, J. T. Lin, W. C. You, E. K. Ng and J. J. Sung (2008). "Screening for gastric cancer in Asia: current evidence and practice." Lancet Oncol 9: 279-287.

Liu, C. Y., C. Y. Wu, J. T. Lin, Y. C. Lee, A. M. Yen and T. H. Chen (2006). "Multistate and multifactorial progression of gastric cancer: results from community-based mass screening for gastric cancer." J Med Screen 13 Suppl 1: S2-5.

Luo, N., L. H. Chew, K. Y. Fong, D. R. Koh, S. C. Ng, K. H. Yoon, S. Vasoo, S. C. Li and J. Thumboo (2003). "Validity and reliability of the EQ-5D self-report questionnaire in English-speaking Asian patients with rheumatic diseases in Singapore." Qual Life Res **12**(1): 87-92

Mabe, K., M. Takahashi, H. Oizumi, H. Tsukuma, A. Shibata, K. Fukase, T. Matsuda, H. Takeda and S. Kawata (2009). "Does Helicobacter pylori eradication therapy for peptic ulcer prevent gastric cancer?" World J Gastroenterol 15(34): 4290-4297.

Mansley, E. C., D. O. Dunet, D. S. May, S. K. Chattopadhyay and M. T. McKenna (2002). "Variation in Average Costs among Federally Sponsored State-Organized Cancer Detection Programs: Economies of Scale?" Medical Decision Making 22(5 suppl): S67-S79.

Mason, J., A. T. Axon, D. Forman, S. Duffett, M. Drummond, W. Crocombe, R. Feltbower, S. Mason, J. Brown and P. Moayyedi (2002). "The cost-effectiveness of population Helicobacter pylori screening and treatment: a Markov model using economic data from a randomized controlled trial." Aliment Pharmacol Ther 16(3): 559-568.

Matsumoto, S., K. Yamasaki, K. Tsuji and S. Shirahama (2007). "Results of mass endoscopic examination for gastric cancer in Kamigoto Hospital, Nagasaki Prefecture." World J Gastroenterol 13(32): 4316-4320.

McAlearney, A. S., K. W. Reeves, C. Tatum and E. D. Paskett (2007). "Cost as a barrier to screening mammography among underserved women." Ethnicity & health 12(2): 189-203.

McCracken, M., M. Olsen, M. S. Chen, Jr., A. Jemal, M. Thun, V. Cokkinides, D. Deapen and E. Ward (2007). "Cancer incidence, mortality, and associated risk factors among Asian Americans of Chinese, Filipino, Vietnamese, Korean, and Japanese ethnicities." CA Cancer J Clin 57(4): 190-205.

McHorney, C. A. and A. R. Tarlov (1995). "Individual-patient monitoring in clinical practice: are available health status surveys adequate?" Qual Life Res 4(4): 293-307.

Menn, P. and R. Holle (2009). "Comparing three software tools for implementing markov models for health economic evaluations." Pharmacoeconomics 27(9): 745-753.

Ministry of Health, S. (2004). Singapore Burden of Disease Study 2004. singapore, Ministry of Health, Singapore

Ministry of Manpower (2010). Report on Labour Force in Singapore 2009: Statistical Tables. Singapore, Ministry of Manpower.
Miyamoto, A., S. Kuriyama, Y. Nishino, Y. Tsubono, N. Nakaya, K. Ohmori, K. Kurashima, D. Shibuya and I. Tsuji (2007). "Lower risk of death from gastric cancer among participants of gastric cancer screening in Japan: a population-based cohort study." Prev Med 44(1): 12-19.

Mizoue, T., T. Yoshimura, N. Tokui, Y. Hoshiyama, H. Yatsuya, K. Sakata, T. Kondo, S. Kikuchi, H. Toyoshima, N. Hayakawa, A. Tamakoshi, Y. Ohno, Y. Fujino and S. Kaneko (2003). "Prospective study of screening for stomach cancer in Japan." Int J Cancer 106(1): 103-107.

Morabito, A., G. Carillio and R. Longo (2009). "Systemic treatment of gastric cancer." Crit Rev Oncol Hematol 70(3): 216-234.

Munene, G., W. Francis, S. N. Garland, G. Pelletier, L. A. Mack and O. F. Bathe (2012). "The quality of life trajectory of resected gastric cancer." J Surg Oncol 105(4): 337-341.

Nakama, H., B. Zhang, X. Zhang and K. Fukazawa (2001). "Age-related cancer detection rate and costs for one cancer detected in one screening by immunochemical fecal occult blood test." Diseases of the colon and rectum 44(11): 1696-1699.

Nakashima, H., R. Nagahama, T. Yamamoto and Y. Ohkura (2010). "Mass screening for gastric cancer: how to select patients for endoscopic examination." Gastric Cancer 13(2): 78-83.

Nam, S. Y., I. J. Choi, K. W. Park, C. G. Kim, J. Y. Lee, M. C. Kook, J. S. Lee, S. R. Park, J. H. Lee, K. W. Ryu and Y. W. Kim (2009). "Effect of repeated endoscopic screening on the incidence and treatment of gastric cancer in health screenees." Eur J Gastroenterol Hepatol 21(8): 855-860.

Nunnally, J. C. (1978). Psychometric theory. New York, McGraw-Hill Inc.

Office, N. R. o. D. (2008). Trends In Cancer Incidence In Singapore 1968-2007. Singapore Cancer Registry Report. Singapore, Health Promotion Board Singapore. 7: 191.

Ogura, K., Y. Hirata, A. Yanai, W. Shibata, T. Ohmae, Y. Mitsuno, S. Maeda, H. Watabe, Y. Yamaji, M. Okamoto, H. Yoshida, T. Kawabe and M. Omata (2008). "The effect of Helicobacter pylori eradication on reducing the incidence of gastric cancer." J Clin Gastroenterol 42(3): 279-283.

Parkin, D. M., F. Bray, J. Ferlay and P. Pisani (2005). "Global cancer statistics, 2002." CA Cancer J Clin 55(2): 74-108.

Parkin, D. M., P. Pisani and J. Ferlay (1999). "Global cancer statistics." CA Cancer J Clin 49(1): 33-64, 31.

Parsonnet, J., R. A. Harris, H. M. Hack and D. K. Owens (1996). "Modelling cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer: a mandate for clinical trials." Lancet 348(9021): 150-154.

Pavlik, E. J., J. R. van Nagell, P. D. DePriest, L. Wheeler, J. M. Tatman, M. Boone, S. Sollars, M. K. Rayens and R. K. Kryscio (1995). "Participation in transvaginal ovarian cancer screening: compliance, correlation factors, and costs." Gynecologic oncology 57(3): 395-400.

Peter M. Fayers, D. M. (2007). Quality of life: the assessment, analysis and interpretation of patient-reported outcomes, John Wiley and Sons.

Pharoah, P. D., P. Guilford and C. Caldas (2001). "Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families." Gastroenterology 121(6): 1348-1353.
Ramsey, S. (2007). "Gut check: can cost-effectiveness analysis help eliminate gastric cancer in Asia?" Cancer Epidemiol Biomarkers Prev 16(5): 873-874.

Riboli, E. and T. Norat (2003). "Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk." Am J Clin Nutr 78(3 Suppl): 559S-569S.

Robert, G., J. Brown and L. Garvican (2000). "Cost of quality management and information provision for screening: colorectal cancer screening." Journal of medical screening 7(1): 31-34.

Rugge, M., M. Cassaro, F. Di Mario, G. Leo, G. Leandro, V. M. Russo, G. Pennelli and F. Farinati (2003). "The long term outcome of gastric non-invasive neoplasia." Gut 52(8): 1111-1116.

Rupnow, M. F., A. H. Chang, R. D. Shachter, D. K. Owens and J. Parsonnet (2009). "Cost-effectiveness of a potential prophylactic Helicobacter pylori vaccine in the United States." J Infect Dis 200(8): 1311-1317.

S. L. Eremenco, J. C., K. Webster, Y. Ohashi, G. Y. Locker, G. Pelletier, D. Cella (2004). "FACT-Gastric: a new international measure of QOL in gastric cancer." J Clin Oncol 22(14 Supplement): 755.

Sadighi, S., M. A. Mohagheghi, A. Montazeri and Z. Sadighi (2006). "Quality of life in patients with advanced gastric cancer: a randomized trial comparing docetaxel, cisplatin, 5-FU (TCF) with epirubicin, cisplatin, 5-FU (ECF)." BMC Cancer 6: 274.

Sadighi, S., A. Montazeri, Z. Sedighi, M. A. Mohagheghi and H. Froutan (2009). "Quality of life in patients with gastric cancer: translation and psychometric evaluation of the Iranian version of EORTC QLQ-STO22." BMC Cancer 9: 305.

Saeki, N., H. Ono, H. Sakamoto and T. Yoshida (2013). "Genetic factors related to gastric cancer susceptibility identified using a genome-wide association study." Cancer Sci 104(1): 1-8.

Saitoh, E., Y. Yokomizo, C. H. Chang, S. Eremenco, H. Kaneko and K. Kobayashi (2007). "Cross-cultural validation of the Japanese version of the lung cancer subscale on the functional assessment of cancer therapy-lung." J Nihon Med Sch 74(6): 402-408.

Salaffi, F., M. Carotti, A. Ciapetti, S. Gasparini and W. Grassi (2011). "A comparison of utility measurement using EQ-5D and SF-6D preference-based generic instruments in patients with rheumatoid arthritis." Clin Exp Rheumatol **29**(4): 661-671.

Secker-Walker, R. H., P. M. Vacek, G. J. Hooper, D. A. Plante and A. S. Detsky (1999). "Screening for breast cancer: time, travel, and out-of-pocket expenses." Journal of the National Cancer Institute 91(8): 702-708.

shapiro, J. (1982). "Evaluation as theory testing: An example from Head Start." Educational Evaluation and Policy Analysis,(4): 341-353.

Shikata, K., Y. Kiyohara, M. Kubo, K. Yonemoto, T. Ninomiya, T. Shirota, Y. Tanizaki, Y. Doi, K. Tanaka, Y. Oishi, T. Matsumoto and M. Iida (2006). "A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study." Int J Cancer 119(1): 196-201.

Shimoyama, T., M. Aoki, Y. Sasaki, M. Matsuzaka, S. Nakaji and S. Fukuda (2012). "ABC screening for gastric cancer is not applicable in a Japanese population with high prevalence of atrophic gastritis." Gastric Cancer 15(3): 331-334.

Shiroiwa, T., T. Fukuda and K. Shimozuma (2011). "Cost-effectiveness analysis of trastuzumab to treat HER2-positive advanced gastric cancer based on the randomised ToGA trial." Br J Cancer 105(9): 1273-1278.
Sickles, E. A., W. N. Weber, H. B. Galvin, S. H. Ominsky and R. A. Sollitto (1986). "Mammographic screening: how to operate successfully at low cost." Radiology 160(1): 95-97.

Singapore Cancer Registry (2011). Cancer Survival in Singapore 1968 - 2007. Singapore Health Promotion Board, Singapore

Singapore Cancer Registry Committee (2010). Trends in cancer incidence in Singapore 1968-2007. Singapore Cancer Registry Report. singapore: 191.

Smith, M. W. and P. G. Barnett (2003). "Direct measurement of health care costs." Medical care research and review : MCRR 60(3 Suppl): 74S-91S.

Smyth, E. C., M. Capanu, Y. Y. Janjigian, D. K. Kelsen, D. Coit, V. E. Strong and M. A. Shah (2012). "Tobacco use is associated with increased recurrence and death from gastric cancer." Ann Surg Oncol 19(7): 2088-2094.

Subramanian, S., D. Ekwueme, J. Gardner, B. Bapat and C. Kramer (2008). "Identifying and controlling for program-level differences in comparative cost analysis: lessons from the economic evaluation of the National Breast and Cervical Cancer Early Detection Program." Evaluation and program planning 31(2): 136-144.

Subramanian, S., F. K. L. Tangka, S. Hoover, A. DeGroff, J. Royalty and L. C. Seeff (2011). "Clinical and programmatic costs of implementing colorectal cancer screening: Evaluation of five programs." Evaluation and program planning 34(2): 147-153.

Sung, J. J., S. R. Lin, J. Y. Ching, L. Y. Zhou, K. F. To, R. T. Wang, W. K. Leung, E. K. Ng, J. Y. Lau, Y. T. Lee, C. K. Yeung, W. Chao and S. C. Chung (2000). "Atrophy and intestinal metaplasia one year after cure of H. pylori infection: a prospective, randomized study." Gastroenterology 119(1): 7-14.

Talley, N. J., K. M. Fock and P. Moayyedi (2008). "Gastric Cancer Consensus conference recommends Helicobacter pylori screening and treatment in asymptomatic persons from high-risk populations to prevent gastric cancer." Am J Gastroenterol 103(3): 510-514.

Tanaka, M., E. Ma, H. Tanaka, A. Ioka, T. Nakahara and H. Takahashi (2011). "Trends of stomach cancer mortality in eastern Asia in 1950-2004: Comparative study of Japan, Hong Kong and Singapore using age, period and cohort analysis." Int J Cancer.

Tashiro, A., M. Sano, K. Kinameri, K. Fujita and Y. Takeuchi (2006). "Comparing mass screening techniques for gastric cancer in Japan." World J Gastroenterol 12(30): 4873-4874.

Terwee, C. B., S. D. Bot, M. R. de Boer, D. A. van der Windt, D. L. Knol, J. Dekker, L. M. Bouter and H. C. de Vet (2007). "Quality criteria were proposed for measurement properties of health status questionnaires." J Clin Epidemiol 60(1): 34-42.

Thompson, S. G. and J. A. Barber (2000). "How should cost data in pragmatic randomised trials be analysed?" BMJ 320(7243): 1197-1200.

Tomizawa, M., F. Shinozaki, R. Hasegawa, K. Fugo, Y. Shirai, N. Ichiki, T. Sugiyama, S. Yamamoto, M. Sueishi and T. Yoshida (2013). "Screening Ultrasonography is Useful for the Diagnosis of Gastric and Colorectal Cancer." Hepatogastroenterology 60(123).

Tong, M. C., P. S. Lo, K. H. Wong, R. M. Yeung, C. A. van Hasselt, S. Eremenco and D. Cella (2009). "Development and validation of the functional assessment of cancer therapy nasopharyngeal cancer subscale." Head Neck 31(6): 738-747.

Tramacere, I., E. Negri, C. Pelucchi, V. Bagnardi, M. Rota, L. Scotti, F. Islami, G. Corrao, C. La Vecchia and P. Boffetta (2012). "A meta-analysis on alcohol drinking and gastric cancer risk." Ann Oncol 23(1): 28-36.

Trochim, W. M. K. (2006). "The Multitrait-Multimethod Matrix." Retrieved 12 June, 2012, from http://www.socialresearchmethods.net/kb/mtmmmat.php.

Tsubono, Y., Y. Nishino, I. Tsuji and S. Hisamichi (2000). "Screening for Gastric Cancer in Miyagi, Japan: Evaluation with a Population-Based Cancer Registry." Asian Pac J Cancer Prev 1(1): 57-60.

Tsugane, S. (2005). "Salt, salted food intake, and risk of gastric cancer: epidemiologic evidence." Cancer Sci 96(1): 1-6.

Tsuji, I., A. Fukao, N. Sugawara, T. Shoji, I. Kuwajima and S. Hisamichi (1991). "Cost-effectiveness analysis of screening for gastric cancer in Japan." Tohoku J Exp Med 164(4): 279-284.

Tsuji, I., Y. Tsubono and S. Hisamichi (2001). "[Effectiveness and cost-benefit of screening for gastric cancer in Japan]." Nihon Rinsho 59 Suppl 4: 533-537.

U.S. Environmental Protection Agency (2010). Cost of Illness Hand book Pennsylvania US Environmental Protection Agency.

Uemura, N., S. Okamoto, S. Yamamoto, N. Matsumura, S. Yamaguchi, M. Yamakido, K. Taniyama, N. Sasaki and R. J. Schlemper (2001). "Helicobacter pylori infection and the development of gastric cancer." N Engl J Med 345(11): 784-789.

Urban, N., G. L. Anderson and S. Peacock (1994). "Mammography screening: how important is cost as a barrier to use?" American journal of public health 84(1): 50-55.

Uwer, L., C. Rotonda, F. Guillemin, J. Miny, M. C. Kaminsky, M. Mercier, L. Tournier-Rangeard, I. Leonard, P. Montcuquet, P. Rauch and T. Conroy (2011). "Responsiveness of EORTC QLQ-C30, QLQ-CR38 and FACT-C quality of life questionnaires in patients with colorectal cancer." Health Qual Life Outcomes 9: 70.

van Gils, P. F., H. H. Hamberg-van Reenen, M. van den Berg, L. Tariq and G. A. de Wit (2010). "The scope of costs in alcohol studies: Cost-of-illness studies differ from economic evaluations." Cost effectiveness and resource allocation : C/E 8: 15.

van Stel, H. F. and E. Buskens (2006). "Comparison of the SF-6D and the EQ-5D in patients with coronary heart disease." Health Qual Life Outcomes **4**: 20.

Vannella, L., E. Lahner, J. Osborn, C. Bordi, M. Miglione, G. Delle Fave and B. Annibale (2010). "Risk factors for progression to gastric neoplastic lesions in patients with atrophic gastritis." Aliment Pharmacol Ther 31(9): 1042-1050.

Victorson, D., J. Barocas, J. Song and D. Cella (2008). "Reliability across studies from the functional assessment of cancer therapy-general (FACT-G) and its subscales: a reliability generalization." Qual Life Res 17(9): 1137-1146.

Voutilainen, M. E. and M. T. Juhola (2005). "Evaluation of the diagnostic accuracy of gastroscopy to detect gastric tumours: clinicopathological features and prognosis of patients with gastric cancer missed on endoscopy." Eur J Gastroenterol Hepatol 17(12): 1345-1349.
Wai, C. T., K. G. Yeoh, K. Y. Ho, J. Y. Kang and S. G. Lim (2002). "Diagnostic yield of upper endoscopy in Asian patients presenting with dyspepsia." Gastrointest Endosc 56(4): 548-551.

Walker, D. (2001). "Cost and cost-effectiveness guidelines: which ones to use?" Health policy and planning 16(1): 113-121.

Wang, J., J. C. Yu, W. M. Kang and Z. Q. Ma (2012). "Treatment strategy for early gastric cancer." Surg Oncol 21(2): 119-123.

Ware, J. E., Jr. and B. Gandek (1998). "Methods for testing data quality, scaling assumptions, and reliability: the IQOLA Project approach. International Quality of Life Assessment." J Clin Epidemiol 51(11): 945-952.

Washington, K. (2010). "7th edition of the AJCC cancer staging manual: stomach." Ann Surg Oncol 17(12): 3077-3079.

Watabe, H., T. Mitsushima, Y. Yamaji, M. Okamoto, R. Wada, T. Kokubo, H. Doi, H. Yoshida, T. Kawabe and M. Omata (2005). "Predicting the development of gastric cancer from combining Helicobacter pylori antibodies and serum pepsinogen status: a prospective endoscopic cohort study." Gut 54(6): 764-768.

Webster, K., D. Cella and K. Yost (2003). "The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation." Health Qual Life Outcomes 1: 79.

Weinstein, M. C., B. O'Brien, J. Hornberger, J. Jackson, M. Johannesson, C. McCabe and B. R. Luce (2003). "Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies." Value Health 6(1): 9-17.

Weinstein, M. C., J. E. Siegel, M. R. Gold, M. S. Kamlet and L. B. Russell (1996). "Recommendations of the Panel on Cost-effectiveness in Health and Medicine." JAMA : the journal of the American Medical Association 276(15): 1253-1258.

Whiting, J. L., A. Sigurdsson, D. C. Rowlands, M. T. Hallissey and J. W. Fielding (2002). "The long term results of endoscopic surveillance of premalignant gastric lesions." Gut 50(3): 378-381.

Whiting, J. L., A. Sigurdsson, D. C. Rowlands, M. T. Hallissey and J. W. L. Fielding (2002). "The long term results of endoscopic surveillance of premalignant gastric lesions." Gut 50(3): 378-381.

WHO-CHOICE. (2003). "Prices and useful lives of tradable capital goods." Retrieved june 2010, from http://www.who.int/choice/costs/prices_t1/en/index.html.

Whynes, D. K. and F. O. B. S. T. Nottingham (2004). "Cost-effectiveness of screening for colorectal cancer: evidence from the Nottingham faecal occult blood trial." Journal of medical screening 11(1): 11-15.

Wong, B. C., S. K. Lam, W. M. Wong, J. S. Chen, T. T. Zheng, R. E. Feng, K. C. Lai, W. H. Hu, S. T. Yuen, S. Y. Leung, D. Y. Fong, J. Ho and C. K. Ching (2004). "Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial." JAMA 291(2): 187-194.

Wu, C. W., S. S. Lo, K. H. Shen, M. C. Hsieh, W. Y. Lui and K. P'Eng F (2000). "Surgical mortality, survival, and quality of life after resection for gastric cancer in the elderly." World J Surg 24(4): 465-472.

Wu, C. Y., K. N. Kuo, M. S. Wu, Y. J. Chen, C. B. Wang and J. T. Lin (2009). "Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease." Gastroenterology 137(5): 1641-1648 e1641-1642.

Xie, F., N. Luo, G. Blackhouse, R. Goeree and H. P. Lee (2008). "Cost-effectiveness analysis of Helicobacter pylori screening in prevention of gastric cancer in Chinese." Int J Technol Assess Health Care 24(1): 87-95.

Xie, F., D. O'Reilly, I. L. Ferrusi, G. Blackhouse, J. M. Bowen, J. E. Tarride and R. Goeree (2009). "Illustrating economic evaluation of diagnostic technologies: comparing Helicobacter pylori screening strategies in prevention of gastric cancer in Canada." J Am Coll Radiol 6(5): 317-323.

Yeh, J. M., W. Ho and C. Hur (2010). "Cost-effectiveness of endoscopic surveillance of gastric ulcers to improve survival." Gastrointest Endosc 72(1): 33-43.

Yeh, J. M., C. Hur, K. M. Kuntz, M. Ezzati and S. J. Goldie (2010). "Cost-effectiveness of treatment and endoscopic surveillance of precancerous lesions to prevent gastric cancer." Cancer 116(12): 2941-2953.

Yeh, J. M., K. M. Kuntz, M. Ezzati, C. Hur, C. Y. Kong and S. J. Goldie (2008). "Development of an empirically calibrated model of gastric cancer in two high-risk countries." Cancer Epidemiol Biomarkers Prev 17(5): 1179-1187.

Yeoh, K. G., L. Chew and S. C. Wang (2006). "Cancer screening in Singapore, with particular reference to breast, cervical and colorectal cancer screening." J Med Screen 13 Suppl 1: S14-19.

Yu, C. L., R. Fielding, C. L. Chan, V. K. Tse, P. H. Choi, W. H. Lau, D. T. Choy, S. K. O, A. W. Lee and J. S. Sham (2000). "Measuring quality of life of Chinese cancer patients: A validation of the Chinese version of the Functional Assessment of Cancer Therapy-General (FACT-G) scale." Cancer 88(7): 1715-1727.

Zapka, J. G., A. M. Stoddard, M. E. Costanza and H. L. Greene (1989). "Breast cancer screening by mammography: utilization and associated factors." Am J Public Health 79(11): 1499-1502.

Zhang, Y. Q., R. MacLennan and G. Berry (1984). "Mortality of Chinese in New South Wales, 1969-1978." Int J Epidemiol 13(2): 188-192.

Zhou, H. J., S. C. Li, N. Naidoo, F. Zhu and K. G. Yeoh (2013). "Empirical evidence of the continuing improvement in cost efficiency of an endoscopic surveillance programme for gastric cancer in Singapore from 2004 to 2010." BMC Health Serv Res 13(1): 139.

Zhou, H. J., J. B. So, W. P. Yong, N. Luo, F. Zhu, N. Naidoo, S. C. Li and K. G. Yeoh (2012). "Validation of the functional assessment of cancer therapy-gastric module for the Chinese population." Health Qual Life Outcomes 10: 145.

Zhu, F., M. Loh, J. Hill, S. Lee, K. X. Koh, K. W. Lai, M. Salto-Tellez, B. Iacopetta, K. G. Yeoh and R. Soong (2009). "Genetic factors associated with intestinal metaplasia in a high risk Singapore-Chinese population: a cohort study." BMC Gastroenterol 9: 76.

PUBLICATIONS

Empirical evidence of the continuing improvement in cost efficiency of gastric cancer surveillance
Hui Jun Zhou, SC Li, N Naidoo, F Zhu, KG Yeoh
BMC Health Services Research, 2013 Apr 15;13:139

Validation of the Functional Assessment of Cancer Therapy-Gastric Module for its use in Chinese
HJ Zhou, BY So, WP Yong, N Luo, SC Li, N Naidoo, F Zhu, KG Yeoh
Health and Quality of Life Outcomes 2012 10:145.

A Cost-effectiveness Analysis Evaluating Endoscopic Surveillance for Gastric Cancer for Populations with Low to Intermediate Risk
Hui Jun Zhou, Yock Young Dan, Nasheen Naidoo, Shu Chuen Li, Khay Guan Yeoh
PLoS One. 2013 Dec 27;8(12)

Poster presentation

Empirical evidence of the continuing improvement in cost efficiency of gastric cancer surveillance
ESMO 13th World Congress on Gastrointestinal Cancer
22-25 June, 2011
Barcelona, Spain

APPPENDICES

Questionnaires used in the three studies

Cost Study

Appendix I: Medical Service Consumption Form (self-designed)

Quality of Life Study

Appendix II: Patient Information Sheet & Informed Consent Form (English)
Appendix III: FACT-Ga Questionnaire (English)
Appendix IV: EQ-5D Questionnaire (English)
Appendix V: Patient Information Sheet & Informed Consent Form (Chinese)
Appendix VI: FACT-Ga Questionnaire (Chinese)
Appendix VII: EQ-5D Questionnaire (Chinese)
Appendix VIII: Clinical Data Collection Form (self-designed)

Apprendix I : Medical Service Consumption Form

MEDICAL SERVICE CONSUMPTION FORM

Date of Review: **Study No (SNO):** **Name in Initials:** **Gender** **Age**

Date (dd/mm/yyyy)	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Method of follow up:						
Histology/Biopsy (Y/N)						
Urease (Y/N)						
Accompanied						
HP infection (Y/N)						
OGD Finding Cardia						
Body & Fundus						
Less Curvature						
Greater curvature						
Antrum						
Histology/Biopsy Cardia						
Body & Fundus						
Less Curvature						
Greater Curvature						
Antrum						
Others						
Prescription						
Purpose for OGD						
Comments (adverse events, complications)						
OGD Charge						

Method of follow up: 1> Oesophagogastroduodenoscopy (OGD); 2> Specialist Consultation; 3> Telephone Interview

Abbreviations: CG, chronic gastritis; EG, erosive gastritis; NEG, non-erosive gastritis; AG, atrophic gastritis; IM, intestinal metaplasia; PUD: peptic ulcer disease;

Apprendix II: Patient Information Sheet & Informed Consent Form (English)

STUDY NO.

QL ___ ___ ___ / ___ ___ ___

VALIDATION STUDY OF FACT-Ga AND EQ-5D QUALITY OF LIFE INSTRUMENTS IN PATIENTS WITH GASTRIC CANCER OR AT HIGH RISK BEING SCREENED FOR GASTRIC CANCER IN SINGAPORE CHINESE POPULATION

Patient Information Sheet and Informed Consent Form

1. Principal Investigator

Associate Professor Yeoh Khay Guan
Department of Medicine, National University Hospital
5 Lower Kent Ridge Road
Singapore 119074
Tel: (65) 67795555

2. Purpose of Research Study

You are invited to participate in this research. It is important to us that you first take time to read through and understand the information provided in this sheet. Nevertheless, before you take part in this research study, the study will be explained to you and you will be given the chance to ask questions. After you are properly satisfied that you understand this study, and that you wish to take part in the study, you must sign this informed consent form. You will be given a copy of this consent form to take home with you.

You are invited because you are seeing doctor at surgery clinic or GCEP participant, and you are Chinese 45 years or older.

This study aims to quantify the profile of quality of life (QoL) in Chinese patients with gastric disease. The lives of patients with stomach disease have been affected by symptoms, side effects and complications associated with surgery and adjuvant therapy. An understanding of their life will be of great value to look after the patients better.

Another purpose is to validate EuroQol questionnaire (EQ-5D) and Functional Assessment of Cancer Therapy gastric cancer model (FACT-Ga) in Singapore Chinese. EQ-5D questionnaire has five questions describing your feeling about your own health status. It tells how you think about the overall quality of life. FACT-Ga asks questions about your well-being over the past week. It measures how your life has been affected.

3. Study Procedures

In total, 200 patients from NUH will participate in the study. You will be interviewed face to face once about the quality of your life. It takes 10-20 minutes for you to finish two questionnaires. If you cannot do it on your own, your family members or main caregivers will help you. We will also collect clinical information about the disease in your stomach, such as diagnosis, treatment (surgery and medicine), HP infection and other diseases from your medical case notes. All patient information and data obtained will be kept confidential. There is no follow up required.

4. Who Can Participate

Chinese patients more than 45 years old who meet the following criteria can enter this study:

- Histologically confirmed gastric cell change which requires removal of stomach according to American Joint Committee on Cancer
- Able to have the interview done at least 2 weeks after the operation. This is to remove the impact of pain or inconvenience directly caused by surgery

GCEP subjects who do not have severe gastric cell change can participate in this study too.

However, patients who have severe co-morbidities (e.g. hip fracture) affecting patient's life greatly, or are unable to provide informed consent, should not enrol in this study.

5. What Is Not Standard Care or Experimental in This Study

Measuring QoL score is not a standard care in the management of patients with gastric diseases. This study will validate the QoL instruments so as to pave the way for their potential application in usual medical care.

6. Possible Risks and Discomfort

This study doesn't involve blood test, invasive medical examination or tissue sampling. You will not be required to take any experimental drug either. Therefore, there are no foreseeable physical risks by participating in this research study.

7. Possible Benefits

There is no direct benefit from participation in this study. However, your participation in this study may add to the medical knowledge about quality of life in patient with gastric disease.

8. Confidentiality

All information obtained during this study will be kept strictly confidential. Your records will be identified only as your initials with a study number. No names will be mentioned in the report of any research arising from this study. In the event that the results of this study are published, your identity will remain confidential.

However, NHG Domain-Specific Review Board and Ministry of Health will be granted direct access to inspect your original medical records to check study procedure and data, without making any of your information public. By signing the Informed Consent Form attached, you are authorizing such access to your study and medical records.

9. Compensation

Participation is voluntary. There is no additional cost to or compensation for patients who participate in the study. By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence.

10. Contacts for Questions or Problems

For answers to any questions about the study please contact our principal investigator:

NUH: A/Prof Yeoh Khay Guan,
c/o co-investigator Dr. Brendon Zhou, (PhD student) at 84040042

For an independent opinion of your rights as a research subject, you may contact the NHG Domain Specific Review Board (DSRB) Secretariat:

DSRB secretariat at 64713266 during office hours.

If you have any complaints about this research study, you may contact the Principal Investigator/Principal Investigator's designee or the NHG Domain Specific Review Board Secretariat.

11. Voluntary Participation

Your participation in this study is voluntary. You may stop participating in this study at any time. Your decision not to take part in this study or to stop your participation will not affect your medical care or any benefits to which you are entitled.

STUDY NO.

QL ___ ___ ___ / ___ ___ ___

CONSENT FORM

Protocol Title:

Validation study of FACT-Ga and EQ-5D quality of life instruments in patients with gastric cancer or at high risk being screened for gastric cancer in Singapore Chinese population

Principal Investigator & Contact Details:

Associate Professor Yeoh Khay Guan
Department of Medicine, National University Hospital
5 Lower Kent Ridge Road
Singapore 119074
Tel: (65) 67795555

I voluntarily consent to take part in this research study. I have fully discussed and understood the purpose and procedures of this study. This study has been explained to me in a language that I understand. I have been given ample time to ask any questions that I have about the study, and all questions have been answered to my satisfaction.

Name of Participant	Signature	Date

Witness Statement

I, the undersigned, certify to the best of my knowledge that the participant signing this informed consent from had the study fully explained in a language understood by him/her and clearly understands the nature, risks and benefits of his/her participation in the study.

Name of Witness	Signature	Date

Investigator Statement

I, the undersigned, certify that I explained the study to the participant and to the best of my knowledge the participant signing this informed consent form clearly understands the nature, risks and benefits of her participation in the study.

Name of Investigator/	Signature	Date
ZHOU HUI JUN.	Brenda Tan.	

Apprendix III: FACT-Ga questionnaire (English)

FACT-Ga (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Ga (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Ga (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
Ga2	I am bothered by reflux or heartburn	0	1	2	3	4
HN1	I am able to eat the foods that I like	0	1	2	3	4
Ga6	I have discomfort or pain when I eat	0	1	2	3	4
Ga5	I have a feeling of fullness or heaviness in my stomach area	0	1	2	3	4
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
Ga 12	I have trouble swallowing food	0	1	2	3	4
Ga4	I am bothered by a change in my eating habits	0	1	2	3	4
B6	I am able to enjoy meals with family or friends	0	1	2	3	4
Ga 10	My digestive problems interfere with my usual activities	0	1	2	3	4
Ga9	I avoid going out to eat because of my illness	0	1	2	3	4
Ga7	I have stomach problems that worry me	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4
Ga 14	I am bothered by gas (flatulence)	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
Leu4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

Apprendix IV: EQ-5D questionnaire (English)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

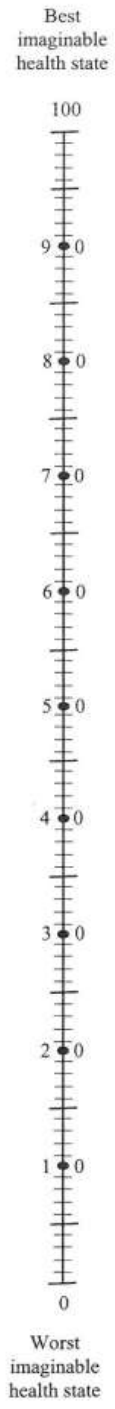
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the **BLACK BOX** below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Apprendix V: Patient Information Sheet and Informed Consent Form (Chinese)

研究编号

QL ___ ___ ___ / ___ ___ ___

FACT-Ga 和 EQ-5D 健康问卷
在新加坡华人胃癌患者和高危人群中的信度和效度研究
（患者知情同意书）

一：项目主要负责人

杨启源教授
新加坡国立大学医院内科
5 Lower Kent Ridge Road
Singapore 119074
联系电话: (65) 67795555

二：研究目的

我们诚邀您参加这项研究。确定你对此同意书内容有正确的理解对我们很重要。即便如此，在您做决定之前，我们还会详细地介绍研究项目。 你可以询问任何问题，直到完全了解研究项目并对问题的答案感到满意为止。如果您最终决定参加，请在这份知情同意书上签字。你本人和我们各留一份以备参考。

邀请您参加是因为你是年纪在 45 岁或以上的华人，来普通外科诊所看病。或者你本人是 GCEP 研究项目的参与者。

本研究是为了量化新加坡华人胃病患者和高危人群的生存和生活质量。胃病患者的生活受多种因素的影响。疾病本身的症状，手术和化疗等治疗的副作用、并发症等都会降低患者的生活质量。所以对胃病患者生存生活质量的研究能提高胃病治疗的整体水平。

此研究的另一目的是检验国际通用的一般生存质量问卷 EQ-5D 和胃癌患者生存质量专门问卷 FACT-Ga，来科学地评价这两量表在新加坡华人群体中的适用性。EQ-5D 只包含 5 个问题，每个问题都是患者对自己健康状况的个人感觉。问卷结果显示您整体生活质量水平。FACT-Ga 询问过去一周中你对自己生活状况的评价。它是测量疾病对生活的影响程度。

三：研究过程

此项研究需要从国大医院收录 200 个病患。每个患者都要和研究者进行一次面对面的交流。交流过程中，您花 10 到 20 分钟独立完成两份健康问卷。如果因种种原因您自己无法独立完成，可让配偶或主要监护人帮忙。我们还需要从您病历中收集如诊断、治疗（手术或化疗）、胃幽门螺旋杆菌感染和其他疾病等临床资料。所有这些资料会严格保密。本研究无需随访。

四：入组条件

新加坡华人 45 岁或以上并满足下列条件者可参加本研究

- 经组织学确认的严重胃部细胞病变，其治疗要求部分或全部胃切除。

研究编号

QL ___ ___ ___ / ___ ___ ___ ___

- 能够在手术后至少两周完成问卷调查。这样做是为了消除手术本身的疼痛不适对患者生活质量的影响。

GCEP 样本人群中无严重胃细胞病变的患者也可以参加这个研究。任何患者如果同时拥有其他严重影响生存质量的疾病和残疾（比如骨折）；或者无法签知情同意书，都不能参加此研究。

五：项目的新颖性和试验性

测量生存质量目前还不是胃病患者的常规诊疗手段。本研究在证实两种生存质量问卷的信度和效度的基础上，为其将来在临床实践中的应用打基础。

六：研究过程可能造成的不适

此项目不涉及抽血、人体组织提取和其他的侵入性医学检查，患者也无需服用任何药品。参加本研究没有任何可预见的伤害。

七：可预计的益处

参加此项研究不涉及直接的利益报酬，但您的参与会提高医生对胃病患者生存质量的认知，并促进这方面的知识更新和发展。

八：患者隐私权维护

任何个人信息都将绝对保密。个人资料只能通过患者英文/拼音名字的首字母缩写以及研究编号来识别。研究报告和项目文件都不提及任何患者的真实姓名。即使研究结果发表了，您的个人信息依然保密。

但是，国立大学医院医学伦理委员会和卫生部有权直接检查您的原始资料，以确保研究者遵守既定研究程序和数据安全。这个检查同样不会暴露您的任何资料。在这份同意书上签字，相当于授权上述监督部门的监督检查行为。

九：回报

本项目基于自愿参加的原则，所以不会造成额外的医疗花费，但也没有金钱实物等形式的报酬。即使在您签署了同意书之后，同样拥有法律保障的权利。如果研究过程中存在医疗差错，您有追究相关责任的权利。

十：项目负责人和联络人

此项目的主要负责人是新加坡国立大学医院内科：

杨启源教授

有关问题请咨询的项目共同研究者，同样也是项目联系人：

周慧君博士 联系电话(手机)： 84040042

研究编号

QL___ ___ ___ / ___ ___ ___

关于此研究的第三方观点，请在办公时间征询国大医院医学伦理委员会

秘书处 联系电话：64713266

如果研究过程当中您产生一些意见和不满，请首先联系项目联系人或主要负责人。如联系不上，请联系国立大学医院医学伦理委员会秘书处。

十一：自愿原则

您是根据个人意愿参加本研究，在研究过程的任何阶段都有权利退出。如果你决定不加入或因种种原因中途退出的话，你的医疗服务和其他权利不会受影响。

研究编号

QL___ ___ ___ / ___ ___ ___

同意书

研究项目：

FACT-Ga 和 EQ-5D 健康问卷在新加坡华人胃癌患者和高危人群中的信度和效度研究

项目主要负责人

杨启源教授
新加坡国立大学医院内科
5 Lower Kent Ridge Road
Singapore 119074
联系电话：(65) 67795555

我自愿参加此同意书所讲的研究项目。在做出决定前我完全明白此项目的研究目的和研究程序。研究者用我理解的语言向我详细解释了项目内容。并给予我足够的时间来询问。我很满意研究者对我所提问题作出的答复。

患者姓名	签字	日期

第三方见证人申明

我，以下签字者，尽我所知证实患者在签同意书之前，研究者以患者理解的语言对研究项目进行了详细的解释。患者清楚研究项目的性质和参加此研究所带来的风险和利益。

见证人姓名	签字	日期

研究者申明

我，以下签字者，尽我所知对患者解释了研究项目。患者在签字之前已清楚研究项目的性质和他/她参加研究所带来的风险和利益。

研究者姓名	签字	日期
Zhou Haijun	Brendon Zhou	

Apprendix VI: FACT-Ga questionnaire (Chinese)

FACT-Ga（第四版）

以下是一些与您患有同样疾病的人所认为重要的陈述。请在每行圈选或标出一个数字来表明适用于您过去 7 天情况的回答。

	生 理 状 况	一点也不	有一点	有些	相当	非常
GP1	我精神不好	0	1	2	3	4
GP2	我感到恶心	0	1	2	3	4
GP3	因为我身体不好，我满足家庭的需要有困难	0	1	2	3	4
GP4	我感到疼痛	0	1	2	3	4
GP5	治疗的副作用使我感到烦恼	0	1	2	3	4
GP6	我觉得病了	0	1	2	3	4
GP7	我因病被迫要卧床休息	0	1	2	3	4

	社 会 / 家 庭 状 况	一点也不	有一点	有些	相当	非常
GS1	我和朋友们很亲近	0	1	2	3	4
GS2	我在感情上得到家人的支持	0	1	2	3	4
GS3	我得到朋友的支持	0	1	2	3	4
GS4	我的家人已能正视我患病这一事实	0	1	2	3	4
GS5	我满意家人间对我疾病的沟通方式	0	1	2	3	4
GS6	我与自己的配偶（或给我主要支持的人）很亲近	0	1	2	3	4
Q1	*不管你近期的性生活的程度，请回答下面的问题* *如果你不愿回答，请在这里注明 □，然后回答下一组问题*					
GS7	我对自己的性生活感到满意	0	1	2	3	4

FACT-Ga（第四版）

请在每行圈选或标出一个数字来表明适用于您过去 7 天情况的回答。

	情感状况	一点也不	有一点	有些	相当	非常
GE1	我感到悲伤	0	1	2	3	4
GE2	我满意自己处理疾病的方式	0	1	2	3	4
GE3	在与疾病的抗争中，我越来越感到失望	0	1	2	3	4
GE4	我感到紧张	0	1	2	3	4
GE5	我担心我可能会去世	0	1	2	3	4
GE6	我担心自己的病情会恶化	0	1	2	3	4

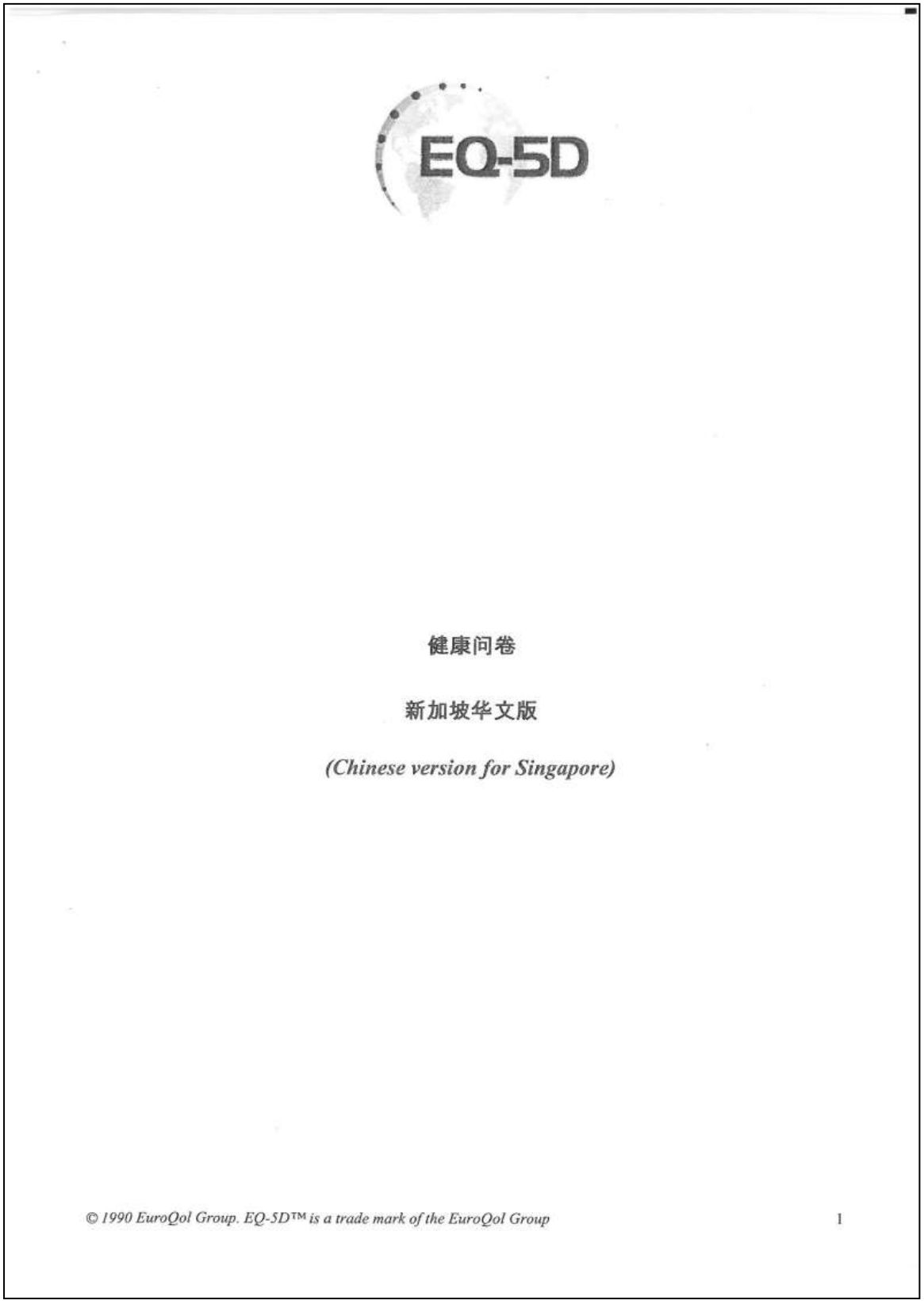
	功能状况	一点也不	有一点	有些	相当	非常
GF1	我能够工作（包括在家里工作）	0	1	2	3	4
GF2	我的工作（包括在家的工作）令我有成就感	0	1	2	3	4
GF3	我能够享受生活	0	1	2	3	4
GF4	我已能面对自己的疾病	0	1	2	3	4
GF5	我睡得很好	0	1	2	3	4
GF6	我在享受我常做的娱乐活动	0	1	2	3	4
GF7	我对现在的生活质量感到满意	0	1	2	3	4

FACT-Ga（第四版）

请在每行圈选或标出一个数字来表明适用于您过去 7 天情况的回答。

	附 加 关 注	一点也不	有一点	有些	相当	非常
C2	我的体重在下降	0	1	2	3	4
Ga1	我的食欲降低	0	1	2	3	4
Ga2	胃反酸或烧心使我烦恼	0	1	2	3	4
HN1	我能够吃我喜欢吃的食物	0	1	2	3	4
Ga6	我吃东西时感到难受或疼痛	0	1	2	3	4
Ga5	我有肚子饱满或沉重的感觉	0	1	2	3	4
C1	我肚子肿胀或绞痛	0	1	2	3	4
Ga 12	我吞咽食物有困难	0	1	2	3	4
Ga4	饮食习惯的变化使我烦恼	0	1	2	3	4
E6	我能享受跟家人或朋友一起吃饭的乐趣	0	1	2	3	4
Ga 10	我的消化问题妨碍我做平常做的事	0	1	2	3	4
Ga9	因为我的疾病，我避免外出吃饭	0	1	2	3	4
Ga7	我担心胃会有问题	0	1	2	3	4
Hep 8	我肚子难受或疼痛	0	1	2	3	4
Ga 14	胀气（肠胃气胀）使我烦恼	0	1	2	3	4
C5	我拉肚子	0	1	2	3	4
An2	我感到累	0	1	2	3	4
HI 12	我觉得全身虚弱无力	0	1	2	3	4
Leu4	因为我的疾病，我计划未来有困难	0	1	2	3	4

Apprendix VII: EQ-5D questionnaire (Chinese)



请在下列各组选项中，指出哪一个句子最能描述您今天的健康状况，并在空格内打勾。

I. 行动

我可以四处走动，没有任何问题。 ❑
我行动有些不便。 ❑
我卧病在床。 ❑

II. 自我照顾

我能照顾自己，没有任何问题。 ❑
我在梳洗、洗澡或穿衣服方面有些问题。 ❑
我无法自己梳洗、洗澡或穿衣服。 ❑

III. 平常活动（如工作、读书、家务、家庭或休闲活动）

我能从事平常活动，没有任何问题。 ❑
我在从事平常活动方面有些问题。 ❑
我无法从事平常活动。 ❑

IV. 疼痛/不舒服

我没有任何疼痛或不舒服。 ❑
我觉得有些疼痛或不舒服。 ❑
我觉得非常疼痛或不舒服。 ❑

V. 焦虑/沮丧

我不觉得焦虑或沮丧。 ❑
我觉得有些焦虑或沮丧。 ❑
我觉得非常焦虑或沮丧。 ❑

为了帮助一般人陈述健康状况的好坏，我们画了一个刻度尺（有点象温度计），在这刻度尺上，100代表您想象中最好的状况，0代表您想象中最差的状况。

我们希望就您的看法，在这个刻度尺上标出您今天健康状况的好坏。请从下面**黑色方框**中画出一条线，连到刻度尺上最能代表您今天健康状况好坏的那一点。

您今天
的
健康状况

Apprendix VIII: Clinical Data Collection Form

Study ID: _____

CLINICAL INFORMATION COLLECTION FORM

(This form should be filled up by interviewer based on casesheets and information from patients and/or their family)

Demographics		Interview Procedure	
DOB (dd/mm/yyyy)		DOI (dd/mm/yyyy)	
Gender		Place of interview	
Language Preferred		Interviewer	
Education		Referral Doctor	
Marriage		Department	
Main Caregiver		Time taken (mins)	
Comments			

Clinical Informaiton

GASTRIC CANCER					
Diagnosis	Date:		Clinical Stage at diagnosis		
	Date:		Clinical Stage after surgery		
	Date:		Histology		
	Date:		Histology		
Comments					
Treatment	(1) Curative (2) Palliative		Currently under treatment		(0) No (1) Yes
Surgery	Date:		Name		
	Date:		Name		
Radiotherapy	DOS		DOE		
	Drug				
	DOS		DOE		
	Drug				
Chemotherapy	DOS		DOE		
	Drug				
	DOS		DOE		
	Drug				
	DOS		DOE		
	Drug				
	DOS		DOE		
	Drug				
Comments					

HP INFECTION				
Diagnosis	Date		OGD (Y/N)	
Treatment	Drug		Duration	
Recurrence	Date		OGD (Y/N)	
Treatment	Drug		Duration	
Comments				

COMOBIDITY					
Rheumatoid Arthritis	Y/N	Diabetes Mellitus	Y/N	Hypertension	Y/N
Ischaemic Heart disease	Y/N	Liver disease	Y/N	Lung disease	Y/N
Renal disease	Y/N	Renal disease	Y/N	Asthma	Y/N
Bleeding disorder	Y/N	CCF	Y/N	ESRF	Y/N
ECOG performance score					

Page 1 of 1